



The History of Neuroscience in  
Autobiography  
Volume 12

Edited by Thomas D. Albright and Larry R. Squire

Published by Society for Neuroscience

ISBN: 978-0-916110-11-6

George F. Koob

pp. 206–246

<https://www.doi.org/10.1523/hon.012005>

*Greg. Koob*



# George F. Koob

## **BORN:**

Okinawa, Japan  
August 29, 1947

## **EDUCATION:**

Pennsylvania State University, BS, Zoology (1969)  
Johns Hopkins University, PhD, Behavioral Physiology (1972)

## **APPOINTMENTS:**

Predoctoral Fellow, Johns Hopkins University, Department of Environmental Medicine (1969–1972)  
Staff Scientist, Department of Neurophysiology, Walter Reed Army Institute of Research (1972–1975)  
Postdoctoral Fellow with Dr. Susan D. Iversen, University of Cambridge, Department of Experimental Psychology, Dr. Leslie Iversen, Medical Research Council, Neurochemical Pharmacology Unit (1975–1977)  
Staff Scientist, Arthur Vining Davis Center for Behavioral Neurobiology, The Salk Institute for Biological Studies (1977–1983)  
Assistant, Associate, Full Adjunct Professor, Departments of Psychology, Psychiatry, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego (1980–2014)  
Associate Member (with tenure), Division of Preclinical Neuroscience and Endocrinology, The Scripps Research Institute (1983–1989)  
Professor, Department of Neuropharmacology, The Scripps Research Institute (1990–2006)  
Director, Alcohol Research Center, The Scripps Research Institute (1995–2014)  
Acting Chair, Department of Neuropharmacology, The Scripps Research Institute (2000–2002)  
Professor and Chair, Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute (2006–2014)  
Director, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health (2014–present)  
Senior Investigator and Section Chief, Neurobiology of Addiction Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health (2014–present)

## **HONORS AND AWARDS (SELECTED):**

Daniel H. Efron Award, Excellence in Research in Neuropsychopharmacology, American College of Neuropsychopharmacology (1991)  
Highly Cited Researcher, Institute for Scientific Information/Web of Science Group, Clarivate Analytics (2001, 2018, 2019, 2021)  
Distinguished Investigator Award, Research Society on Alcoholism (2002)  
Mark Keller Award, National Institute on Alcohol Abuse and Alcoholism (2004)  
Honorary Doctorate of Science, Pennsylvania State University (2009)  
Marlatt Mentorship Award, Research Society on Alcoholism (2012)  
Julius Axelrod Mentorship Award, American College of Neuropsychopharmacology (2012)  
Docteur Honoris Causa, Universite Bordeaux Segalen (2013)  
IPSEN Foundation Neuroplasticity Award (2014)  
Distinguished Scientist Award, American Society of Addiction Medicine (2015)  
Chevalier de la Legion d'Honneur in recognition of outstanding contributions to Franco-American scientific relations (2016)  
National Academy of Medicine (2017)  
Jellinek Memorial Award, Research Society on Alcoholism (2018)

*George Koob has made major contributions to our understanding of the neurobiology of addiction. He has guided nationwide efforts to address the scourge of alcohol use disorder by directing the National Institute on Alcohol Abuse and Alcoholism. His early research focused on the neurobiology of stress and drug reward and then evolved into understanding neuroadaptations of the brain stress and reward systems in the progression to compulsive-like drug seeking. He hypothesized that hyperkatifeia is driven by allostatic changes of loss of reward and gain of stress neuroadaptations to drive and perpetuate the cycle of addiction through negative reinforcement. These advances provide a bridge to a key motivational component of the real-world misery of addiction and have implications for how humans experience negative emotional states in general.*

# George F. Koob

I was born in a Quonset hut in Okinawa, Japan, on August 29, 1947, the son of Robert Anthony Koob from East Rutherford, New Jersey, and Theodora Johanna Koob (née Foth) from Jersey City, New Jersey. I was the oldest of four children. Kathy, my younger sister, tragically died of non-Hodgkin's lymphoma at the age of 46. My mother and father met in Carlstadt, New Jersey, and married in 1942. My father was subsequently drafted into the U.S. Army to serve in World War II, and he participated in the invasion of Okinawa as a warrant officer in the 305th Ordinance Battalion. He won a commission as second lieutenant after the cessation of hostilities with Japan. He went on to obtain a bachelor's degree and master's degree in business administration at Babson Institute and ultimately pursued a career as a regular Army officer. After 32 years, he retired from the Army as a full colonel at Fort Campbell, Kentucky, where he served as comptroller for the base that houses the 101st Airborne Division. My mother was a teacher, professor of English, and writer. My mother earned her PhD in linguistics in 1946 from New York University and joined my father on Okinawa in 1946. There, she founded the U.S. Dependent school system on Okinawa, which remains to this day, and served as its first principal. Theodora subsequently wrote and published eight children's books and was recruited as a professor of English at Shippensburg State College in Shippensburg, Pennsylvania, in 1964. She retired in 1980. Throughout her career, she taught at the grade school, junior high school, senior high school, and university levels.

## The Early Years

I grew up as an Army brat and had a rich intellectual but socially tumultuous upbringing as we moved every one to three years, from Okinawa to Aberdeen, Maryland (my first grade); Fort Bragg, North Carolina (second grade); Natick, Massachusetts (third grade); Angouleme, France (fourth to sixth grades); Augusta, Georgia (seventh and eighth grades); and finally Chambersburg, Pennsylvania (ninth to twelfth grade). I had two younger brothers (Joe and Steve) and a younger sister (Kathy). We were always challenged by our parents to pursue academic careers. There was never any doubt that each of us would go to college and that I would go on to pursue an advanced degree. Joe became a college professor of music, motivational speaker, and writer. Steve became a conservator archaeologist and curator of glass at the Corning Glass Museum. Kathy became a textile conservator. Despite moving every one to three years throughout my youth, there were many constants, mostly within our family unit as we regularly gained and

lost childhood friends because of my father's frequent Army reassignments. My mother insisted on music lessons and the pursuit of hobbies for each of us. Mine was collecting butterflies (which was not, alas, an ecologically appropriate choice). My father was a dedicated Boy Scout leader who won every award they conferred—he was most proud of his Silver Beaver Award. My brothers and I all joined the Boy Scouts and earned the rank of Eagle Scout. Looking back, the wonderful experiences of Boy Scout camps, a time when we really connected with our father, contributed to my later career in physiology and avocation of gardening (more on that later). Another plus of my being an Army brat was the extraordinary and wonderful opportunities to travel and see new places. My mother took us everywhere in France, with the American military base near Angoulême as the launching point. From the castles of the Loire to real caves of Lascaux to opera in Bordeaux, I was imprinted early on as a devout Francophile and even developed an ear for the French language, having to learn the catechism in French for my second French First Communion.

In high school, I had a particularly charismatic biology teacher, Louise Grove, who was also my Latin teacher. I became enthralled with both subjects. Salient during this time was teaching the discovery of the DNA structure by Watson and Crick and the beginning of lay books on ethology, such as *Territorial Imperative* by Robert Ardrey. I was equally fascinated by the classics and actually was accepted as a classics major at Pennsylvania State University but changed at the last minute to zoology. My brother, Steve Koob, became the classics major and went on to a brilliant career as a conservator/archeologist.

## Pennsylvania State University, 1965–1969

My studies at Pennsylvania State University during the first year were at the Mont Alto campus, which was 10 miles from our house in Chambersburg. This afforded a more gradual transition to the large campus at State College and allayed some of the costs. I remember a beautiful wooded campus, dedicated teachers, and a harrowing drive in some very large snow storms. I enjoyed such subjects as botany and zoology but struggled with calculus. Probably most important was that I was able to skip the regular first English courses at Penn State and took the advanced English course, which was taught by a charismatic teacher who challenged students with literature from Dostoevsky to Shakespeare, honing our ability to think critically and integrate concepts. I aced the final with a Blue Book essay on how love transcended as a key element across all of what we had read that term (more on my writing in my graduate years below).

The move to the Penn State main campus for my sophomore year was a culture shock of sorts, given all the opportunities to meet new people and make new friends. But alas, I eventually settled in to studying. During that

second year, I met members of the Alpha Zeta fraternity, which was an honorary fraternity with origins in agriculture but included many members with aspirations for related careers in zoology, veterinary medicine, landscape architecture, and even medicine. I pledged the fraternity and was elected. We had a fraternity house in the center of campus, right next to Recreation Hall. One had to maintain a 3.0 (B) academic record, and we were a dry house (no alcohol). Here, I made lifelong friends and acquired a yearning for gardening that evolved into my current main avocation of growing exotic fruit trees in Southern California.

My move to the main campus of Penn State allowed my choice of a zoology major to flourish. Here, my undergraduate advisor was the famous ecologist David E. Davis. He guided me to courses in physiology and psychology, which dovetailed nicely with my early interests in ethology. I looked to join the primate work of a Penn State professor who divided his time between the University of Georgia and Penn State, but the timing was off and he was at the University of Georgia. One of my psychology professors, Michael Warren, sent me to Howard S. Hoffman, who was studying the power of imprinting to shape operant conditioning. He had baby ducklings imprinted to a milk bottle that moved back and forth on a train track (Hoffman et al., 1972). Needless to say, I was fascinated. Howard Hoffman immediately assigned me to reading Ferster and Skinner (1957) and to working with Ivan Divac, two events that presaged my ultimate career pursuit of bridging behavior and the brain. I also worked through the summers doing paid jobs at Penn State, cleaning rabbit cages and helping study wild rats. One series of events that I noted retrospectively was that I excelled in all courses on physiology at Penn State while my fraternity brothers often struggled with them. There was never any doubt that I would apply to graduate school and pursue a career in academia, something likely related to animal behavior.

But there was a cloud on the horizon. The Vietnam conflict became fully engaged, and the draft was activated in the United States. I drew a low draft number and was clearly facing the draft upon graduation. Then "The Colonel" (my father) intervened. In the spring of my second year at Penn State, I received a phone call one afternoon from the Colonel who directed ROTC at Penn State. Unbeknownst to me, my father had enrolled me in ROTC, and I was to report to training the next day. However, I quickly figured out that there was a program that allowed one to delay active duty after being commissioned in the officer core to attend graduate school, making ROTC training much more palatable. To qualify, I ultimately had to graduate one term early from Penn State in the spring of 1969 and was commissioned as a second lieutenant in the U.S. Army Signal Corps. Meanwhile, I had applied to five graduate schools to pursue studies in ethology. I was called for an interview for the Pathobiology Program in the School of Public Health at Johns Hopkins University in Baltimore, Maryland. Unfortunately,

they had no slots available on their training grant, so they negotiated with the Department of Environmental Medicine for a slot on their National Institutes of Health Heart and Lung training grant. I poignantly remember my interview with the chair of Environmental Medicine, Richard Riley, who was questioning my transcript and pointed out a few C grades intermixed with mostly A and B grades. He specifically asked about my C grades in map reading from my ROTC courses. I answered that ROTC had not been my highest priority for study, to which he smiled and said he was against the war and I would be welcomed to his department.

## Johns Hopkins University, Graduate School, 1969–1972

My graduate career in the Department of Environmental Medicine began in April 1969. I graduated with my PhD in June 1972. I worked continuously throughout that period, including all summers, to meet the Army's time requirement of how long active duty could be delayed by attending graduate school. Upon joining the Johns Hopkins program, I immediately did a rotation with Charles Southwick, exploring mouse behavior and doing ecological field work on the Chesapeake Bay, and in a course with Edwin Gould, I trained bats to run down a runway to obtain mealworms. At the same time, I was assigned to Stephen Weinstein and Zoltan Annau, who had a program that explored the effects of hypoxia on motivated behavior, including brain stimulation reward. Zoltan Annau had trained with Jim Olds, the codiscoverer of brain stimulation reward with Peter Milner (Olds and Milner, 1954). We embarked on measuring brain stimulation reward concomitantly with food and water intake over long periods to account for the long-term effects experienced by humans who move to high altitude. This study led to my first *eureka!* moment and my first published scientific paper (Koob et al., 1970). I define a *eureka!* moment as one of those results in an experiment that was unpredicted and leads to a completely different conceptual direction. Here, we found that rats that were exposed to 10% oxygen (equivalent to about 18,000 feet above sea level) exhibited a profound and prolonged increase in lever pressing for brain stimulation reward that we assumed reflected a euphoric-like response, particularly given that orally administered amphetamine at a large dose produced an identical effect. Both hypoxia and amphetamine also reduced responding for food and water. I went on to show that this effect was not mediated by peripheral sympathetic activation, including a heroic adrenal demedullation surgical procedure, and hypothesized it was attributable to central nervous system monoamine dysregulation, including my first catecholamine assay (Koob and Annau, 1973, 1974). During this period, Stephen Weinstein left academia for business, and Zoltan Annau became my PhD adviser. I learned much about basic physiology and behavior from Zoltan and much about the excitement of new findings that science provides. During this period,

my interest in ethology faded, and my interest in what was to be the new field of the neuroscience of emotion and motivation blossomed. Zoltan also stimulated my future career not only with erudite guidance of my thesis project but also with his strong encouragement to interact with world-class scientists at Johns Hopkins. Zoltan was also rigorous about experimental design, statistics, and writing. When my first scientific paper came back from him covered in red ink, he, a Hungarian by birth, remarked that “if I did not know better, one might think that English was not your first language.” Ultimately, my first paper (revised) was read by Philip Bard, who had a wonderful story about the paradoxical effects of opioids in cats. My first event recorder was borrowed from Curt Richter, deemed by many as the father of physiological psychology. I often saw Curt Richter, Anna Baetjer, Philip Bard, and Vernon Mountcastle, all towering figures in their fields, in the lunchroom at the top of the Johns Hopkins School of Public Health. I took psychiatry at the Johns Hopkins Medical School. I so enjoyed the section by Joe Brady that I took his graduate course on behaviorism, and he ultimately became the chair of my thesis committee. I took Solomon (Sol) Snyder’s neuropharmacology course, and he ultimately advised us on our amphetamine brain stimulation studies. Both Joe and Sol became my career-long guardian angels, opening doors and advising me throughout my career. All of them—Zoltan, Joe, and Sol—planted the seeds of a career that involved understanding the neurochemical/neurocircuitry of how the brain mediates motivation and emotions.

Indeed, my early interactions with Joe Brady illustrate this motivational imprinting. I remember one day after his demonstration of operant conditioning to the medical school psychiatry course, where he trained chickens to walk off the end of a large table, I queried him by asking, “Dr. Brady, how hungry were those chickens?” His response: “Koob, damn hungry.” This interaction contributed to my lifelong interest in motivation and what drives behavior.

However, as my PhD neared completion, and thus the completion of my delay of my active duty in the U.S. Army, the dark cloud that hung over my generation had not dissipated. I was commissioned as a second lieutenant in the Army Signal Corps, a combat branch. My goal, at the advice of Joe Brady among others, was to fulfill my service obligation in the Medical Service Corps at the Walter Reed Army Institute of Research (WRAIR) in Washington, D.C. To accomplish this, I had to be moved from the Signal Corps to the Medical Service Corps, a task for which I enlisted the aid of three Army Colonels: Joe Brady (who introduced me to the Division of Neuropsychiatry at WRAIR), Harry Holloway (director of the Division of Neuropsychiatry at WRAIR), and my father (who followed my paperwork). By the summer of 1972, I received my orders to report to Fort Sam Houston in San Antonio, Texas, for officer basic training in the Medical Service Corps. I joined WRAIR in the fall of 1972.



## Walter Reed Army Institute of Research, 1972–1975

Now a captain in the Medical Service Corps, I was assigned as a staff scientist to the Department of Neurophysiology at WRAIR where my director was Herb Spector. However, I quickly began to work also with Jim Meyerhoff, who had studied with Sol Snyder at Johns Hopkins. I was very keen to pursue studies of the role of key brain catecholamine circuits in reward using the brain stimulation reward technique that was developed in my thesis work. A highly influential series of papers published by Tim Crow and colleagues (Anlezark et al., 1973; Crow, 1973) generated great interest that I conveyed to Jim Meyerhoff and two other colleagues and collaborators, Jean Balcom (Kant) and Rufus Sessions. At WRAIR, I was able to set up a bank of operant chambers, procure a PDP-8 computer, and take a course in Maynard, Massachusetts, on how to program the computer. We generated a number of salient findings, including showing that heroin facilitated brain stimulation reward (Koob et al., 1975), charting the projections of dopamine neurons in the ventral tegmental area (Koob et al., 1975), and finding that the locus coeruleus seemed more involved in stress-like responses than reward and learning (Sessions et al., 1976). The intellectually rich environment at WRAIR provided an equally important direction in my career. Here, I worked as a teaching assistant with Jim Petras in the human neuroanatomy course at WRAIR. Michie Vane, who had worked with Walle Nauta, taught me numerous neuroanatomical staining procedures, including Nauta-Gygax silver staining. Jim Petras introduced me to Harvey Karten, Sven Ebbesen, Walle Nauta, Lennart Heimer, and Floyd Bloom. My introduction to Floyd Bloom was especially notable. I had been so interested in the locus coeruleus that I was keen to know the afferent inputs to the locus coeruleus. I pestered Jim Petras to introduce me to Floyd. I had heard him give a seminar on his elegant work on norepinephrine in the hippocampus. I thought that if anyone knew afferents to the locus coeruleus, then it would be him. When Jim Petras called Floyd at his National Institute of Mental Health laboratory at St. Elizabeth's Hospital in Washington, D.C., Floyd immediately wanted to know who was asking and then asked Jim to put me on the phone. I introduced myself as George Koob, "K-O-O-B, book spelled backwards," something my father always said. Floyd laughed for what seemed like minutes and that was the beginning of a lifelong mentorship and friendship. He invited me to all their research seminars at St. Elizabeth's Hospital, and I visited them regularly. What I found out later was that he was looking for someone in behavioral neuroscience to join their group. These collaborations and interactions left me with a thirst to receive further training in functional neuroscience. I had thought of working in Paris with Jacques Glowinski, but Sol Snyder instead suggested a postdoctoral stage at the University of Cambridge, England, a position for which I was accepted. Just before leaving for Cambridge, at one of the last visits to

Floyd Bloom's group, he asked me what my plans were upon my return to the United States from Cambridge. I remarked that I had no plans as of yet. He said he would like me to join their group, either in D.C. or possibly at The Salk Institute in La Jolla, California.

### University of Cambridge, 1975–1977

For me, my postdoctoral stage at the University of Cambridge was magical. Where else could one live in Grantchester and on the way to work walk past the cows in the fens, through the gardens of a 700-plus-year-old college (Pembroke), and past the Eagle Pub where Watson and Crick declared that they had found the secret of life. In the summer of 1975, Susan (Sue) Iversen had offered me a position as a postdoctoral fellow in her group in the Department of Experimental Psychology at the University of Cambridge. Shortly thereafter, I won an R21 grant from the National Institute of Mental Health to pursue postdoctoral studies in Sue's laboratory. I combined both sources of funds and was able to stay in Cambridge from 1975 to 1977. A fellowship offer had later come from the University of Bordeaux, but I decided to go to Cambridge. My French connection would flourish later. My time at Cambridge was probably my most formative from the perspective of shaping the framework for my life's work to understand the neurochemical neurocircuitry of motivation. The openness, generosity, and hospitality of Sue and her husband, Leslie, as well as my friends and collaborators at Cambridge, including Trevor Robbins, Barbara Sahakian, Paul Fray, Piers Emson, and Claudio Cuello, created a standard to which I have aspired ever since. More important, the thirst for knowledge and the framework of trying to understand how the brain worked via neurochemical neurocircuits were enduring legacies imparted on me particularly by Sue and Les Iversen.

Upon my arrival at Cambridge, my first charge was to work with Les, who directed the Medical Research Council research unit, called the Neurochemical Pharmacology Unit (NCPU) at Cambridge, to improve the catecholamine assay and move it to psychology. Just before Christmas 1975, we successfully improved the assay using paper chromatography. My participation in this effort earned me a high table dinner for Candelmas Feast with Les at Trinity College, a wonderful evening never to be forgotten. With Sue, I investigated the functional significance of norepinephrine and dopamine in motivation in a series of studies that used intracerebral administration of the catecholamine neurotoxin 6-hydroxydopamine and dopamine receptor antagonists. In parallel, I collaborated with many students and faculty in psychology and the NCPU, many of whom became lifelong friends. My work with Sue Iversen resulted in a paper on how stress-induced eating sustains learning (also with Paul Fray; Koob et al., 1976) and a key study that showed that the destruction of dopamine projections produced

persistent and pronounced deficits in intracranial self-stimulation from ipsilateral electrodes in both lateral hypothalamus and locus coeruleus groups but only transient effects on self-stimulation from contralateral electrodes at these sites (Koob et al., 1978a). Sue had insisted that I do some teaching in the context of tutorials. Both Sue and Trevor Robbins, a demonstrator at Cambridge (equivalent to the U.S. academic ranking of assistant professor), patiently taught me basic principles of general psychology so that I could be an effective tutor. In turn, I taught all of what I knew about brain dissection and surgical techniques. Ultimately, my collaboration with Trevor emerged into an enduring, lifelong, and intellectually fruitful friendship. I like to think that our brains fed off each other in our early attempts to understand the role of the mesolimbic dopamine system in motivated behavior. The arguments ranged from reward to conditioned reinforcement to incentive motivation, resulting in a series of papers that anticipated our future pursuits. We showed that nucleus accumbens dopamine depletion decreased activation that was associated with the anticipation of food in hungry rats (Koob et al., 1978b) and later blocked schedule-induced polydipsia (Robbins and Koob, 1980). Later, Trevor introduced me to Barry Everitt, and another lifelong friendship developed. With Trevor and Barry, we first outlined the neurocircuitry of addiction in the context of dysfunctional domains in a chapter for the textbook (Koob et al., 2008) where I assiduously wedged in the circuitry of the negative emotional state of drug withdrawal (more on that to come). Trevor, Barry, and I subsequently had many theoretical discussions that helped shape my view of addiction and significantly broadened my perspectives on addiction.

As my time in Cambridge neared 18 months, Sue Iversen brought me into her office. She wondered if I had been thinking of what I would do when my funds for working with her ran out. She noted that she was seeing a significant number of positions opening in the United States and asked if Floyd had written to me yet. He had not. But that week, after my meeting with Sue, a blue airmail letter arrived from Floyd, offering me a position as a research associate, then staff scientist, in the Arthur Vining Davis Center for Behavioral Neurobiology at The Salk Institute. That July, I arrived in La Jolla and joined the Bloom lab.

### The Salk Institute, 1977–1983

My arrival was heralded by my colleagues from the University of Cambridge, including Sue and Les Iversen, who then visited every summer for several years after that. Their presence eased my transition into a completely new world of outstanding biologists and neuroscientists. I immediately set up a single operant chamber and began establishing an operant conflict test with the goal of studying the intoxicating effects of alcohol as Floyd challenged us to participate in winning an Alcohol Research Center (ARC) grant to study

the neurobiology of alcohol. There was very little known about the neurobiology of alcohol in 1977. In fact, a prevailing hypothesis at that time was that alcohol acted mainly like an anesthetic that interfered with membrane dynamics. I poignantly remember the site visit for the ARC grant, chaired by Joe Brady from Johns Hopkins University. After his bear hug of a greeting, he announced he would see me at my second thesis defense, alluding to the fact that he had chaired my PhD thesis defense. The site visit went well, and the study of the neurobiology of alcohol has paralleled my studies of the neurobiology of addiction in general. Both of these pursuits further opened windows on my search to understand the neurobiology of motivation.

Two separate tracks of research preoccupied me in these early years at Salk. First, the arrival of David Roberts as a postdoctoral fellow from the University of British Columbia in Canada introduced us to intravenous drug self-administration. Here, we replicated a key finding from Dave's PhD thesis that removal of the dopamine projection to the nucleus accumbens with the neurotoxin 6-hydroxydopamine produced a pronounced decrease in intravenous cocaine self-administration and produced an extinction-like pattern of behavior (Roberts et al., 1980). David Roberts worked with both me and Floyd, as did many of my earlier postdoctoral fellows. This shared mentoring structure with Floyd Bloom endured while I was at Salk and beyond. Notably, this type of shared mentoring reversed as my career grew, with fellows primarily trained by junior faculty also asking to be comentored by me via collaboration. The drug addiction and motivation work continued with results showing convergence of the role of dopamine and opioid mechanisms for opioid- and psychostimulant-induced locomotor activation and reward in the nucleus accumbens (Pettit et al., 1984). At the same time, we mounted significant refutation of the hypothesis of Roy Wise that dopamine was the reward neurotransmitter (Ettenberg et al., 1982). In a series of studies, we argued that dopamine was key to psychostimulant reward and played a major role in incentive motivation (i.e., more of a functional role in the activation of behavior anticipating reward; Koob, 1982; Koob, 1992). This debate raged for years and to some extent presaged the concept of incentive salience, which probably best explains the functional role of the dopamine system (Robinson and Berridge, 1993). A vignette from this period amply illustrates the argument. Roy Wise had given the Bloom laboratory a talk on his dopamine reward hypothesis, and I had countered with a rebuttal. The final word came from Floyd when he said, "I do not know, Roy. If you ever followed a Parkinson's patient into the bathroom to take a piss, you know they are motivated." Roy and I finally buried the hatchet in our shared commentary in *Neuropsychopharmacology* in 2014 (Wise and Koob, 2014).

At the same time and in parallel, we began to explore measures of alcohol intoxication to ultimately study the neuropharmacological/neurocircuitry mechanisms that mediate alcohol reward. Early on, we adopted an incremental shock conflict test (Pollard and Howard, 1979) that reli-

ably proved sensitive to alcohol. In a series of studies in collaboration with Karen Thatcher-Britton, professor in the Department of Psychiatry at the University of California, San Diego (UCSD), we identified an anxiety-like role for corticotropin-releasing factor (CRF; Thatcher-Britton and Koob, 1986), proconflict effects of a benzodiazepine receptor inverse agonist that was being touted as an “alcohol antagonist” (Britton et al., 1988), and powerful anticonflict effects of neuropeptide Y (NPY; Heilig et al., 1992). These studies ultimately led to our parallel efforts to examine the neural substrates that mediate alcohol self-administration in rodents. Here, we adopted a sweet solution fadeout procedure from Hank Samson (Samson, 1986) to initiate drinking at levels that generated reliable blood alcohol levels (Koob and Weiss, 1990). Indeed, our CRF and NPY work and the animal model development of Karen Thatcher-Britton, Markus Heilig, Emilio Merlo-Pich, Friedbert Weiss, and Amanda Roberts, among many others, provided the foundation for the ultimate transition to studying neuroadaptations that drive excessive drug taking.

Another research program we developed at The Salk Institute came from Floyd’s becoming very interested in the functional roles of neuropeptides in the brain. We began work on  $\beta$ -endorphin, showing that when it was injected in the ventral tegmental area, it produced robust locomotor activation (with Luis Stinus), presumably by activating the mesolimbic dopamine system (Stinus et al., 1980). At that time, Floyd wondered about studies from David De Wied and colleagues in The Netherlands that showed dramatic behavioral effects of vasopressin and vasopressin-like peptides in facilitating memory (De Wied, 1976; Walter et al., 1978). At the same time, a confluence of factors converged to move neuropeptide studies into high gear. Norman White joined us on sabbatical from McGill University and prompted us to utilize established animal models of memory in our studies of the effects of peripherally administered neuropeptides. Soon afterward, a watershed moment in my career arrived. Michel Le Moal from the University of Bordeaux came to work with us in the summer of 1978. He had regularly joined the laboratory of Jim Olds at Caltech in Pasadena, California, for his annual summer visit to a U.S. laboratory. In the summer of 1976, however, Jim had passed away, and Michel asked Floyd if he could join the Bloom laboratory at Salk for the summer to work with me. This was the beginning of another lifelong collaboration and friendship that has endured for more than 40 years. Michel Le Moal became my foremost experimental and conceptual collaborator.

The ensuing Koob-French connection then became one of the most enduring and pleasurable experiences of my research career. I learned to speak French fluently by living with my French colleagues in their homes, specifically Herve Simon early on and Michel Le Moal when he bought a townhouse near the medical center. Herve and his wife, Marianne, not only taught me to speak French but also taught me to cook, and I still have my

cherished copy of *Cuisine San Souci* (Montigny and Kahn, 1977) though its cover is torn. Luis Stinus and Robert Dantzer became dear friends and collaborators as well, introducing me to new exciting dimensions of science and additional myriad elements of French culture. I actually gave several science lectures exclusively in French, including a plenary talk at the French Society for Neuroscience. Ultimately, I mentored 13 French postdoctoral fellows and seven French visiting scientists in my laboratories at Salk and The Scripps Research Institute (TSRI). I am very proud of winning an honorary doctorate from the University of Bordeaux and the French Legion of Honor, but considering Michel Le Moal as my “French brother” and the enduring friendships and wonderful immersion in the rich French culture are what I value most from my French connection.

After our first successful summer exploring the functional role of neuropeptides, Michel invited me to Bordeaux, thus beginning an annual spring/summer exchange. I worked in Bordeaux with Michel’s group at Institut National de la Sante et de la Recherche Medicale (INSERM) and Centre National de la Recherche Scientifique (CNRS) units in April to May, and Michel worked with us at Salk (and later at Scripps) each summer for six weeks, every year from 1978 until 2005 when administrative responsibilities precluded long visits for both of us. We won support for this exchange for nine years from the National Science Foundation and CNRS. Finally, the return of Roger Guillemin to Salk and the move of the Wylie Vale group to the temporary building space between the Salk main building and the Glider Port near campus, which housed my first laboratory, provided us with an unending source of contact, discussions, novel neuropeptides, and collaborations. What evolved were again long-term collaborations and personal friendships with Catherine Rivier, Jean Rivier, and Wylie Vale that were key to our studies on the function of brain stress systems and that provided cultural delights. Wylie became a never-ending source of non-science-related book reading recommendations, and Jean and I went on frequent fruit tree foraging expeditions to expand our burgeoning gardening avocations.

On the neuropeptide front, Michel and I successfully replicated the prolongation of extinction in rats that is produced by subcutaneous vasopressin administration and went on to show that we could reverse such effects with doses of a vasopressin antagonist that also reversed vasopressin-induced blood pressure activation (Le Moal et al., 1981). This was followed by numerous studies and collaborations with the Bordeaux group, with the conclusion that the neuropeptide vasopressin has both an interoceptive arousal function in the periphery and a parallel arousal effect in the brain, independent of the periphery (Le Moal et al., 1984; Lebrun et al., 1985; Le Moal et al., 1987). Later, this role of vasopressin came to be understood as part of brain stress systems, with significant data suggesting that vasopressin 1b receptor antagonists have antistress/anxiolytic-like effects in animal models (Griebel et al., 2002).

In 1981, a second *eureka!* moment occurred. Wylie Vale, Catherine Rivier, Jean Rivier, and Jochem Speiss at Salk sequenced the 41-amino-acid CRF, the long-awaited neuropeptide that drove the release of adrenocorticotrophic hormone and subsequent adrenal steroid response to arousal and stress (Vale et al., 1981). Marvin Brown had already seen preliminary evidence of a neurotropic action of intraventricular CRF administration producing sympathetic activation (Brown et al., 1982). With Wyle's urging, Michel Le Moal and I designed an experiment to test the hypothesis that CRF had a neurotropic action in the brain to facilitate behavioral responses to stress. We injected CRF at three doses intracerebroventricularly and observed behavior and locomotor activity in well-habituated rats. We observed dose-dependent activation, even with climbing on the walls of the wire mesh test cages. We also observed some very peculiar behavior, expressed as forepaw treading and tremor-like behavior. I called Wylie and told him the rats were "levitating," and he came over to watch. Later, in a more stressful open-field environment, the rats exhibited a dose-dependent increase in sensitivity to the inhibitory effects of the open field (Sutton et al., 1982). We later learned that at high doses, CRF could produce electroencephalographic activation that is associated with seizures. Altogether, these findings supported the hypothesis that CRF plays a neurotropic role in the brain to facilitate behavioral responses to stress.

Thus, my time at The Salk Institute began my two-track independent research programs, one exploring the neurobiological substrates of motivation and drug reward and the other exploring the functional role of endogenous neuropeptides. These research programs interacted but never fully merged until later, in what I consider a third *eureka!* moment after we moved to TSRI. During this period, I was joined by a number of postdoctoral fellows under my tutelage, including Aaron Ettenberg, Franco Vaccarino, Marianne Amalric, and Christine LeBrun (the latter two from France). My first PhD student, Neal Swerdlow, also joined, who was a walk-on from the UCSD Medical School.<sup>1</sup> We explored the neural and neuropharmacological substrates for the reinforcing effects of psychostimulants, opioids, and alcohol, with a focus on dopamine and opioid peptides converging on the nucleus accumbens.

## The Scripps Research Institute, The First Half, 1983–1997

In 1983, Floyd Bloom decided to move his laboratory to The Scripps Clinic and Research Foundation (renamed later TSRI), forming the Division of Preclinical Neuroscience and Endocrinology in the Department of Basic

<sup>1</sup>(1977–1983) Predoctoral fellow: Neal Swerdlow. Postdoctoral fellows: David C.S. Roberts, Aaron Ettenberg, Jeffrey Schwartz, Derek van der Kooy. Visiting Scientists: Norman White, Michel Le Moal, Trevor Robbins, Charles Ksir.

and Clinical Research, then chaired by Ernie Beutler. Floyd was particularly intrigued by the burgeoning field of molecular biology and its potential application for discovering previously unknown neurotransmitters/neuromodulators and their receptors and functions in the brain. His studies began with Greg Sutcliff at TSRI, and this approach ultimately resulted in a number of discoveries, including isoforms of myelin-associated glycoprotein (Lai et al., 1987) and the neuropeptide hypocretin (de Lecea et al., 1998). I was invited to join Floyd's lab in this move and was offered a position as associate member (equivalent to associate professor) with tenure, which I readily accepted.

Joining TSRI also marked the point at which both my independent addiction and stress research programs began to merge. Accomplishments that moved us toward the conceptual merge were studies of output neurocircuitry that mediates psychostimulant and opioid reward (Hubner and Koob, 1990; Robledo and Koob, 1993), the establishment of a role for dopamine and opioid peptides in the nucleus accumbens in alcohol reward (Rassnick et al., 1992; Heyser et al., 1999), and confirmation that CRF had a neurotropic function in the central nervous system to mediate behavioral responses to stress and that CRF receptor antagonists block behavioral responses to stressors (Tazi et al., 1987; Swerdlow et al., 1989; Heinrichs et al., 1992).

The ultimate merging of these two research tracks came from five breakthroughs that comprised several *eureka!* moments. The first centered on studies that showed that motivational aspects of drug withdrawal (anxiety-like and aversive-like effects of drug withdrawal) could be reversed by CRF receptor antagonists. The second was an unexpected finding, in which the nucleus accumbens was implicated in the motivational effects of opioid withdrawal (Koob et al., 1989). The third was conceptualizing neuroadaptations that are associated with addiction, which was published in *Science* in 1988 (Koob and Bloom, 1988). The fourth was stimulated by my teaching an undergraduate course at UCSD, when I recognized a common pattern of behavioral dysregulation across all addictions. The fifth came from maturation of my collaboration with Michel Le Moal to the theoretical level, where he introduced me to the concept of allostasis.

For the first major breakthrough, in a clever use of microdialysis and radioimmunoassay, in which the perfusion medium contained anti-CRF serum, Emilio Merlo-Pich, a Fogarty fellow, was able to measure CRF in the central nucleus of the amygdala (CeA) in freely moving animals. He showed a dramatic increase in extracellular CRF in the CeA during alcohol withdrawal (Merlo-Pich et al., 1995). Similar results were found by others in the bed nucleus of the stria terminalis (BSNT; Olive et al., 2002). Extracellular CRF also increased in the CeA during precipitated withdrawal from chronic nicotine (George et al., 2007), withdrawal from binge cocaine self-administration (Richter and Weiss, 1999), and withdrawal from opioids (Weiss et al., 2001) and cannabinoids (Rodriguez de Fonseca et al., 1997). Equally



compelling, we were able to reverse the anxiogenic-like effects and aversive effects of alcohol, opioids,  $\Delta^9$ -tetrahydrocannabinol (THC), and nicotine withdrawal with systemic, intracerebroventricular, and intracerebral administration of CRF receptor antagonists (Rassnick et al., 1993; Baldwin et al., 1991; Grieder et al., 2014; Rodriguez de Fonseca et al., 1997).

The second major breakthrough came from the results of an experiment in which we sought to identify potential targets in the brain that mediate motivational aspects of opioid withdrawal with Tamara Wall, an honors student from UCSD, and Floyd Bloom (Koob et al., 1989). The literature had suggested that somatic signs of precipitated opioid withdrawal in rats, such as wet dog shakes and ptosis, were mediated by opioid receptors in such regions as the medial thalamus and periaqueductal gray. However, when we used an operant measure of malaise associated with precipitated opioid withdrawal, the suppression of lever pressing for food pellets and increased sensitivity to the response-disruptive effects of an intracerebrally injected opioid receptor antagonist showed that opioid receptors in the region of the nucleus accumbens were far and away the most sensitive site relevant to the medial thalamus and periaqueductal gray. Thus, I realized that the nucleus accumbens, which was known to be important for the positive reinforcing effects of opioids, also may be responsible for the response-disruptive, aversive stimulus properties of opioid withdrawal. We argued that “euphoria” and “dysphoria” that are induced by opioids may reflect opponent motivational processes that operate at the cellular level within the nucleus accumbens. The specter of opponent process theory penetrated my thinking and moved my research from studying how drugs produce their acute positive reinforcing effects to how drug addiction is driven by negative reinforcement.

For the third breakthrough in 1988, Floyd Bloom was invited to write a review on addiction for *Science*, and he asked me to do it with him. The paper (Koob and Bloom, 1988) was one of the first attempts to attach neurocircuit changes to adaptations that are associated with repeated drug seeking and taking. In a sense, we applied what we knew about the neurobiology of repeated exposure to drugs of addiction to the opponent process theory of Richard Solomon (Solomon and Corbit, 1974; Solomon, 1980), which we took one step further. We hypothesized that tolerance and dependence resulted from two types of neuroadaptations: within-system neuroadaptations and between-system neuroadaptations. In the paper, we established a framework that has held up over time and provided a heuristic framework to identify key elements of the addictive process:

In a within-systems opposing process, the primary cellular response element to the drug would itself adapt to neutralize the drug's effects; persistence of the opposing effects after the drug disappears would produce the withdrawal response ...

In the between-systems opposing process, a different cellular system and separable molecular apparatus would be triggered by the changes in the primary drug response neurons and would produce the adaptation and tolerance. (Koob and Bloom, 1988, 720)

The fourth breakthrough was initiated early upon my arrival to San Diego in 1977. I had met and was befriended by J. Anthony “Tony” Deutsch, a professor of psychology at UCSD. Somewhere around 1979–1980, Tony offered to let me help him teach undergraduates. I ultimately began teaching a course he taught called Drugs, Addiction, and Mental Disorders. Tony was an endless source of intellectual discussion about various topics related to motivation. Perhaps ultimately the most rewarding for me, he introduced me to exotic fruit gardening in San Diego County by supplying me with everything from figs to cherimoyas to tropical guavas. This evolved into a significant avocation, where we currently care for more than 150 varieties of fruit trees and have fruit year-round on our property in Rancho Santa Fe, California.

I enjoyed teaching so much that I created two undergraduate courses: Drugs and Behavior and Impulse Control Disorders. I also created the graduate-level psychopharmacology course. My teaching had two other major benefits to my career: (1) enabling me to explain the meaning of what I did in research with regard to translation to the human condition, and (2) allowing UCSD undergraduate students to join our laboratory for independent study and honor research thesis projects. Almost all the research assistants we hired over my tenure at TSRI were former students with independent research projects. However, it was with the creation in 1997 of my course Impulse Control Disorders, which used as a background framework the principles of self-regulation outlined in the book *Losing Control* (Baumeister et al., 1994), that I began to see a common pattern of phenotypes that we collectively term “addiction,” whether an addiction to drugs or a nondrug addiction (or “process addiction”; e.g., gambling). I realized that addiction inevitably involves a repeated three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation.

The fifth breakthrough again came through an invitation from Floyd Bloom, then Editor-in-Chief of *Science*, that Michel Le Moal and I write a review on addiction entitled, “Drug Abuse: Hedonic Homeostatic Dysregulation” (Koob and Le Moal, 1997). Here, for the first time, all our thinking about addiction converged, and we characterized addiction as a chronically relapsing disorder, characterized by loss of control and compulsive drug seeking within a heuristic framework comprising a three-stage addiction cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. We integrated the addiction cycle with elements of the diagnostic criteria for substance dependence from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (American Psychiatric

Association, 1994), with the elements of self-regulation failure and with hypothesized neurochemical mechanisms (Koob and Le Moal, 1997). My participation in an episode of the documentary series directed by Bill Moyers, *The Hijacked Brain* (season 1, episode 2, *Addiction: Close to Home*, 1998), where I explained my perspective on addiction to a lay audience, also helped me consolidate my thinking on the hedonic dysregulation that was caused by addiction. During this period from 1983 to 1997, a large number of outstanding postdoctoral fellows (38) and visiting scientists (12) had passed through the Koob lab.<sup>2</sup>

### The Scripps Research Institute, The Second Half, 1998–2014

Our role and integration at TSRI grew during this period, and ultimately Floyd formed the Department of Neuropharmacology in 1990. In 1990, I was promoted to professor in the Department of Neuropharmacology. From 2002 to 2004, I served as Acting Chair of the Department of Neuropharmacology. Then in 2006, to consolidate and coordinate our work on the neurobiology of addiction and at the suggestion of the president of TSRI, Richard Lerner, we formed the department-level Committee on the Neurobiology of Addictive Disorders. I then served as a professor and the Chair until leaving to become Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2014.

At this point, approximately midway through my research career, my initial research programs on drug reward, neuropeptides, and stress converged, and all of my energy began to focus on what we termed the negative emotional side (or “dark side”) of addiction and how such negative emotional states drive negative reinforcement to contribute to the compulsive drug-seeking and drug-taking characteristics of addiction. More *eureka!* moments awaited, which were now directed at the role of stress and negative emotional states in addiction.

My next *eureka!* moment occurred when Serge Ahmed, my postdoctoral fellow from Bordeaux, decided to test the hypothesis that extended access to cocaine would prolong extinction to cocaine. Rats were divided into two

<sup>2</sup>(1984–1997) Predoctoral fellows: Lisa H. Gold, Athina Markou, Stefanie Rassnick, S. Barak Caine, Brian A. Baldo, Shelly S. Watkins, Darrel Macey. Postdoctoral fellows: Franco J. Vaccarino, Tom Blasco, Marianne Amalric, Christine Lebrun, Matthew B. Weinger, Abdeloughhab Tazi, Carol Hubner, Friedbert Weiss, Belinda J. Cole, Luigi Pulvirenti, Helen Baldwin, Rafael Maldonado, S. Stevens Negus, Markus Heilig, Stephen C. Heinrichs, Patricia Robledo, Emilio Merlo-Pich, Athina Markou, Frederique Menzaghi, Michelle D. Brot, Gery Schulteis, Loren H. Parsons, Petri Hyytia, Carmen Maldonado-Vlaar, Mark P. Epping-Jordan, Ana Maria Basso, Amanda J. Roberts, Francoise Dellu-Hagedorn, Charles J. Heyser, Yvette Akwa, Mariarosa Spina, Amanda D. Smith, John R. Walker, Michael R. Weed, K. Noelle Gracy, Serge H. Ahmed, Vincent David, Angelo Contarino. Visiting Scientists: Luis Stinus, Martine Cador, Joe Martinez, Keith Matthews, Luigi Pulvirenti, Angela Roberts, S. Mechiel Korte, Barry Everitt, Fernando Rodriguez de Fonseca, Bo Soderpalm, Regina Richter, Victor A. Molina.

groups: one with access to intravenous cocaine self-administration for 1 hour (short-access group) and one with access to intravenous cocaine self-administration for 6 hours (long-access group). An escalation in intake was observed only in the long-access group with the increase in intake observed during not only during the first hour of the session, but also sustained over the entire session and an upward shift of the dose-effect function. When the animals were allowed access to different doses of cocaine, both the long- and short-access animals titrated their cocaine intake, but long-access rats consistently self-administered almost twice as much cocaine at any dose tested, suggesting a decrease in reward or increase in hedonic threshold in the escalated animals (Ahmed and Koob, 1998). Such an escalation in intake was then observed by us not only for cocaine but also for methamphetamine, heroin, and nicotine and in alcohol-dependent animals (Kitamura et al., 2006; Chen et al., 2006; Cohen et al., 2012; Roberts et al., 2000). Confirming the hypothesized set point change was the observation that intracranial self-stimulation thresholds increased in parallel with the escalation of cocaine (Ahmed et al., 2002), methamphetamine (Jang et al., 2013), and heroin (Kenny et al., 2006). While no animal model fully replicates the panoply of symptoms that are associated with drug addiction in humans, animals with extended access to drug, in effect, meet most of the criteria associated with addiction, including tolerance, withdrawal, substance taken in larger amounts and over a longer period than intended, and elements of compulsive-like drug seeking, thus providing a powerful means of examining the neuroadaptations driving compulsive-like drug seeking (Edwards and Koob, 2013; George et al., 2014).

As such, extended access to drugs of abuse and dependence-induced alcohol drinking have provided significant insight into the role of stress-related neurotransmitter neuromodulators in driving compulsive drug seeking. For alcohol, intracerebroventricular administration of a CRF<sub>1</sub>/CRF<sub>2</sub> receptor antagonist blocked the increase in alcohol self-administration during acute withdrawal from alcohol vapor-induced dependence in rats, but CRF receptor antagonists had no effect on alcohol self-administration in nondependent animals (Valdez et al., 2002). When administered directly into the CeA, the same CRF receptor antagonist blocked the increase in alcohol self-administration in dependent rats (Funk et al., 2006). These data suggest an important role for CRF, primarily within the CeA, in mediating the increase in self-administration that is associated with dependence. We also found that CRF receptor antagonists, injected intracerebroventricularly or systemically, blocked potentiated anxiety-like responses to stressors during protracted abstinence (Breese et al., 2005; Valdez et al., 2003) and the increase in alcohol self-administration that is associated with protracted abstinence (Valdez et al., 2002; Chu et al., 2007), similar to results reported by others (Sommer et al., 2008; Gehlert et al., 2007).

Critical to these studies was another of my long-standing collaborations with my colleagues at the University of Bordeaux. Luis Stinus had

established a robust conditioned place aversion paradigm using three chambers and a central triangular area. Luis and I, with Gery Schulteis (my postdoctoral fellow), then went on to show that this paradigm produced robust conditioned place aversion to very low doses of naloxone (4–8  $\mu\text{g}/\text{kg}$ ) injected subcutaneously in opioid-dependent rats (Schulteis et al., 1994). We went on to show that such place aversion lasted for weeks once established (Stinus et al., 2000) and was sensitive to blockade by CRF receptor antagonists (Stinus et al., 2005). In a study of the suppression of operant responding as an index of withdrawal malaise, naloxone precipitated an aversive response after a single morphine injection (Schulteis et al., 1997). These studies together pointed to long-lasting conditioned responses to neuroadaptation in hedonic systems (aversive responses) that occurred early in the addiction process, much earlier than had been previously thought.

CRF<sub>1</sub> receptor small-molecule receptor antagonists also selectively reduced the increase in alcohol self-administration associated with withdrawal (Funk et al., 2007). CRF receptor antagonists also blocked the increase in intake that was associated with extended access to the intravenous self-administration of cocaine (Specio et al., 2008), nicotine (George et al., 2007), heroin (Greenwell et al., 2009; Park et al., 2015), and food (Cottone et al., 2009).

During this period, around 1999–2000, one of my postdoctoral fellows, Noelle Gracy, took a position with Academic Press/Elsevier, and she commissioned Michel Le Moal and me to write a book on the neuroscience of addiction, which was finally published as the *Neurobiology of Addiction* in 2006 (Koob and Le Moal, 2006). Then, in 2014, in collaboration with Michael (Mike) Arends (who began working with me as an undergraduate research student in 1994 and became instrumental to my publishing efforts ever since), we wrote a college-level textbook called *Drugs, Addiction, and the Brain* (Koob et al., 2014). Because of the enormity of research generated on the neurobiology of addiction in the 10 years since publication of *Neurobiology of Addiction* in 2006, we embarked on writing an update, which blossomed into a series of five volumes. As of this writing, three of these volumes are published—*Neurobiology of Addiction: Volume 1. Introduction to Addiction* (Koob et al., 2019), *Neurobiology of Addiction: Volume 2. Psychostimulants* (Koob et al., 2020a), and *Neurobiology of Addiction: Volume 3. Alcohol* (Koob et al., 2021)—and the next two volumes (Opioids and Nicotine/Cannabis) are well underway.

A key to success in any endeavor requires skills from many quarters. Since 1994, Mike Arends has served as my own editor in chief, polishing my writing and correcting all errors since that time (more than 600 peer-reviewed articles and book chapters). He also took on managing editor roles for two journals for which I served as Editor-in-Chief: *Pharmacology, Biochemistry and Behavior* and *Journal of Addiction Medicine*. Mike has also aided me tremendously since the mid-1990s with salient literature searches that are integral to my writing, to the point that I included him as a coauthor on

books I have written with Michel Le Moal, including *Drugs, Addiction, and the Brain* (Koob et al., 2014) and the *Neurobiology of Addiction* series. With his invaluable help, I am afforded the time to focus on writing, thinking, and synthesizing. He continues to be instrumental and to make substantive contributions to my success.

The research results and our conceptual evolution generated over this period led Michel and me to refine our thinking about a more prominent role for neuroadaptations in brain stress systems as one progresses through the stages of the addiction cycle. Here, we added to our conceptualization of the hedonic dysregulation associated with drug addiction by invoking the contribution of an anti-reward system and the role of negative reinforcement (Koob and Le Moal, 2008). A further part of this thesis was that a key part of addiction involves long-term, persistent dysregulation of the activity of neural circuits that mediate anti-reward motivational systems that derive from two sources: a decrease in the function of brain reward systems that normally mediate natural rewards (within-system neuroadaptations) and recruitment of brain stress systems (between-system neuroadaptations), both of which drive aversive states (Koob and Le Moal, 2008). We argued that such anti-reward neuroadaptations represent the opponent process state that is hypothesized to be triggered by the excessive activation of brain reward systems that forms a general feature of biological systems (Solomon, 1980). The development of the aversive emotional state that drives the negative reinforcement of addiction was conceptualized as the “dark side” of addiction (Koob and Le Moal, 2005). Thus, drug seeking in the binge/intoxication stage was hypothesized to largely involve positive reinforcement. As hedonic allostasis develops, an additional source of motivation, negative reinforcement, is recruited, in which the individual engages in compulsive drug seeking and drug taking to relieve withdrawal symptoms (Koob and Le Moal, 2008).

In 2010, Nora Volkow, director of the National Institute on Drug Abuse (NIDA), and I were asked by the journal *Neuropsychopharmacology Reviews* to review the literature on the neurocircuitry of addiction. Here, we bridged what was known about the neurocircuitry of addiction from both preclinical data from animal models of addiction and neuroimaging data from human studies to the three-stage cycle framework and provided a heuristic basis for studying the neurobiology of addiction (Koob and Volkow, 2010).

Around this time and in a different context with two anesthesiologists, Joe Shurman at Scripps Memorial Hospital and Howard Gutstein at MD Anderson Cancer Center, we attempted to explore why some individuals who take prescription opioids progress to opioid addiction (Shurman et al., 2010). Our hypothesis was that opioid misuse in the context of pain management produces hypersensitivity to emotional distress. Our thesis was that opioid withdrawal consisted of a major negative emotional state that is characterized not just by physical symptoms and physical pain but also by

negative emotional symptoms that are associated with opioid withdrawal and alcohol and drug withdrawal in general, including chronic irritability, physical pain, emotional pain, malaise, dysphoria, alexithymia, and the loss of motivation for natural rewards. These symptoms could be engaged if a subject took opioids at levels above those needed to address acute pain (Shurman et al., 2010). In this context, I decided to create my own word—*hyperkatifeia*, defined as the increased intensity of the constellation of negative emotional/motivational symptoms and signs observed during withdrawal from drugs of abuse (hypersensitive negative emotional state)—to parallel the word hyperalgesia, which described a hypersensitive pain state. Both hyperkatifeia and hyperalgesia were hypothesized to be generated by opioid withdrawal (Shurman et al., 2010).

Thus, the compulsive drug seeking that is associated with addiction is hypothesized to derive from multiple sources of motivational dysregulation that occur in three functional domains that reflect the three stages of the addiction cycle: incentive salience/pathological habits in the binge/intoxication stage, negative emotional states in the withdrawal/negative affect stage, and executive function deficits in the preoccupation/anticipation stage (Everitt and Wolf, 2002; Koob and Volkow, 2010). These three domains and stages are hypothesized to be mediated by three major neuro-circuitry elements: basal ganglia, extended amygdala, and prefrontal cortex, respectively. The hyperkatifeia that drives negative reinforcement is hypothesized to derive from the loss of function of key neurochemical circuits within the brain reward system in the basal ganglia and gain of function within the brain stress systems (CRF, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroimmune factors) in the extended amygdala. Compelling evidence exists to argue that hyperkatifeia that is triggered by acute excessive drug intake is sensitized during the development of compulsive alcohol taking with repeated withdrawal, persists into protracted withdrawal, and contributes to the development and persistence of the compulsive loss of control of drug seeking. Again, all this work was facilitated by a large number of outstanding postdoctoral fellows (34) and visiting scientists (8) who had passed through the Koob lab from 1998 to 2014.<sup>3</sup>

<sup>3</sup>(1998–2013) Predoctoral fellows: Glenn Valdez, Paula Park, Cara Buck. Postdoctoral fellows: Monique Vallee, Cristina Orsini, Daniel Lin, Emanuela Izzo, Andrew Morse, Ahmed Alomary, Joseph Lewis, Marc Azar, Eric Zorrilla, Benjamin Boutrel, Scott Chen, Heather Richardson, Cindy Funk, Sandy Ghozland, Brendan Walker, Tom Greenwell, Valentina Sabino, Pietro Cottone, Sunmee Wee, Chitra Mandyam, Nicholas Gilpin, Laura Orio, Dong Ji, Olivier George, Kaushik Misra, Candice Contet, Scott Edwards, Leandro Vendruscolo, Timothy Whitfield, Ami Cohen, Joel Schlosburg, Carrie Wade, Brooke Schmeichel, Michel Verheij. K99 awardees: Valentina Sabino, Pietro Cottone, Nicholas Gilpin, Sunmee Wee, Scott Edwards, Marian Logrip, Joel Schlosburg. Visiting Scientists: Miguel Navarro, Dale L. Birkle, Koki Inoue, Antoine Tabarin, Serge Ahmed, Osamu Kitamura, Olivier Halfon, Olivier Deschaux.

On a personal note, from 1994–2014, I raised my son, Cameron Michel Koob, who went on to Franklin and Marshall College, graduated and worked in politics helping with the Democratic National Committee and a number of political candidates, including Tom Steyer’s campaign for president. He is currently a Georgetown University law school student, aspiring to a career in corporate law with a possible focus on the biomedical domain.

At this point, my career had made a full circle. I had returned to the original findings of my PhD thesis that hypoxic stress facilitated reward. I reflected on the relationship between reward and stress and two towering figures from the field of psychology who influenced my early career, Horsley Gantt from the Pavlovian tradition and Joseph Brady from the operant tradition (Gantt, 1942; Brady, 1956; Koob, 2017). Their observations that conflict and aversive stimuli can result in emotional-like responses imprinted me in how aversive stimuli can motivate behavior in the form of negative reinforcement and how this process forms the basis for a major part of the pathophysiology of addiction. Thus, as observed by Louis Pasteur, in a sense, my PhD training supported the argument, “In the fields of observation, chance favors only the prepared mind” (Louis Pasteur lecture, University of Lille, December 7, 1854).

So how did my graduate studies at Johns Hopkins with Zoltan Annau prepare me to go from the positive reinforcement studies in the first half of my career to negative reinforcement studies in the second half of my career? In my PhD thesis studies, we identified a role for catecholamines in how mild to moderate stress can facilitate brain reward systems. Sol Snyder introduced me to how drugs of abuse profoundly activate brain reward systems. Perhaps as part of the rich tradition of the study of reinforcement, from both classical and operant conditioning perspectives, Horsley Gantt and Joseph Brady laid the conceptual groundwork for motivation and emotion that resonated with me and prepared me to recognize that the converse could also be true: excess reward can engage homeostatic mechanisms to regulate motivation. However, when Michel Le Moal and I embraced Richard Solomon’s opponent process theory, with an overlay of allostasis, the neurocircuitry of the emotional states that were described by Gantt and Brady were unveiled.

During this period, I took on some significant administrative responsibilities. Floyd Bloom became editor in chief of *Science* in 1995, and I replaced him as director of the NIAAA-funded Alcohol Research Center at TSRI from 1995 to 2014, carried through four 5-year renewals. In 2001, I successfully won an NIAAA consortium grant, Integrative Neuroscience Initiative on Alcoholism (INIA), and served as consortium coordinator from 2001 until 2014, successfully renewing it twice. In 2006, I formed the Committee on the Neurobiology of Addictive Disorders at TSRI. During my tenure as director of the TSRI ARC, we began to focus on the neurobiology of alcohol use disorder (AUD) at multiple levels of analysis, from molecular to cellular to neuropharmacology to neurocircuitry. In parallel with our changing



conceptual framework, we moved from studies on the acute intoxicating effects of alcohol to the neuroadaptations associated with the development of dependence. A significant advance was developing an animal model of dependence-induced drinking using a chronic intermittent ethanol exposure procedure. Another major advance was to focus molecular and cellular studies on brain circuits that are relevant to the engagement of excessive drinking in dependence. We also began examining the role of not only GABA and glutamate neurotransmission but also their interaction with neuropeptides in the extended amygdala in the negative emotional state and stress associated with alcohol dependence. Finally, while directing the TSRI ARC, I developed the concept of the “Center at Large” to expand the ARC to be a resource for alcohol research across the whole San Diego community to recruit new young investigators and disseminate alcohol-related information in community outreach.

Some of the original goals of the INIA consortium were to first identify gene targets that are produced by excessive drinking in animal models, nominated by expression assays or other methods, and then to confirm gene targets using transgenic, knockout, inducible knockout, site-specific knockout, RNAi, *in situ* hybridization, *in vivo* electrophysiology and imaging, and next-generation sequencing. Another goal was to attract new and innovative investigators to the field of alcohol research by recruiting individuals for U01 grants and Pilot Projects and making informatics-integrated datasets accessible, searchable, and interactive with other databases for all scientists who are interested in alcoholism research. When I handed the reins of INIA over to R. Adron Harris at the University of Texas, Austin, in 2014 to then become director of NIAAA, the consortium had evolved even further. New goals included the identification of druggable targets that would be the most promising for medications development for the treatment of AUD.

Significant progress was made on all the goals of INIA and centered on the refinement and standardization of animal models of excessive drinking, identification of new gene targets for excessive drinking, and implementing novel approaches for functional validation. Extensive gene expression studies using gene arrays were completed on genetic and behavioral models of excessive drinking. Three major functional gene pathways were identified, providing novel gene targets: neuroinflammation, ion channels, and second messenger systems. A key result was the finding of a significant number of genes that are related to neuroimmune function that are activated in a transcriptome meta-analysis across INIA (Mulligan et al., 2006). Subsequent studies supported a key role for neuroimmune function with chronic alcohol exposure, ultimately leading to this part of INIA being termed INIA-Neuroimmune (Blednov et al., 2011). Other major contributions of INIA to the field included the development, refinement, and standardization of excessive drinking animal models so that they reliably produce blood alcohol levels greater than 100 mg% and can be widely used in interactive

studies across INIA, including the development of an animal model of binge-like drinking in mice (drinking in the dark; Rhodes et al., 2005). Novel approaches to functional validation that were introduced within INIA were the use of next-generation transcriptome sequencing and the design and production of viral vectors for RNAi knockdown and the development of knockout mice and rats. Additionally, numerous outstanding neuroscientists were recruited to the alcohol field, thereby broadening and diversifying the scientific base. Thus, using NIAAA's INIA consortium approach, the discovery of neuroimmune and other alcohol targets based on cross-species genomic, cellular, and behavioral neuroadaptations across different laboratories has systematically allowed the identification of conserved signaling pathways that are associated with AUD (Harris and Koob, 2017). This approach to neuroscience has provided the field with rigorous replicable measures for translation to the human condition and a heuristic framework advancing treatment strategies.

However, my interest in translational research had earlier roots with another conceptual breakthrough that originated with Barbara Mason at the University of Miami. She was the principal investigator on the U.S. multicenter clinical trial launched by Lipha Pharmaceuticals for the ultimate approval of acamprostate for the treatment of AUD. I was recruited to the team to help coordinate preclinical evidence of the mechanism of action of acamprostate from our own studies and those across the world (De Witte et al., 2005). Through these interactions, I came to learn about innovative human laboratory strategies for translation that were initiated by Barbara (Mason et al., 2008). She showed the efficacy of nalmefene, an opioid receptor antagonist, in treating alcoholism in a four-year double-blind study (Mason et al., 1999). She also directed the pivotal U.S. study for the approval of acamprostate for the treatment of AUD (Mason et al., 2006). She had developed a highly innovative and pioneering human laboratory paradigm for the development of medications for AUD using cue reactivity under conditions of different emotional settings in alcohol-dependent subjects (Mason et al., 2008). Her studies have shown that the response to drugs in the human laboratory paradigm is predictive of efficacy in clinical trials (Mason et al., 2009; Mason et al., 2014). Given our extensive studies identifying targets for the development of medications for AUD, Barbara and I decided to join forces and won support for the funding of a joint grant in 1999 on medication development in protracted abstinence in alcoholism, which was renewed several times until I left for NIAAA in 2014. Barbara validated her human model of craving with existing medications, and then we "translated" a number of novel compounds from the preclinical model of excessive drinking during withdrawal during chronic intermittent alcohol exposure in rodents to the Mason human laboratory study paradigm. Successful compounds from this work included gabapentin (Mason et al., 2014) and mifepristone (Vendruscolo et al., 2015). Her human laboratory

approach is now being widely adopted in the field and should facilitate the development of medications for all drug addictions. Perhaps more importantly, this collaboration led to a conceptual breakthrough, what we called the Rosetta Stone approach, in which we hypothesized that existing pharmacotherapies for addiction could be used to validate and improve animal and human laboratory models to identify viable new treatment candidates (Koob et al., 2009). Barbara not only provided me with a conceptual framework for the movement of my career to translational neuroscience—she also helped me understand the clinical syndrome of addiction and the suffering such patients experience. During this period, I began a series of lectures at a local private treatment facility, Casa Palmera, in Del Mar, California, founded and run by Lee Johnson. With Barbara's help, I was able to translate my brain science to patients, helping them understand that their conditions were treatable and that recovery was possible. My collaborations with Barbara also contributed to the clinical "top-down" impetus for the emphasis on negative emotional states and stress as driving forces of addiction and a key neglected opportunity for treatment targets (Koob and Mason, 2016).

At the same time, Barbara became my muse, intellectual sounding board, best friend, and soul mate. Floyd Bloom recruited Barbara to TSRI as the Pearson Family Professor in 2007, and our relationship flourished, and we fell in love. We have lived together since 2013, and we married in Fiji on February 14, 2018. Barbara is currently professor at Scripps Research, The Pearson Family Professor, Director of the Pearson Center for Alcoholism and Addiction Research, director of the TSRI Alcohol Research Center (the same one founded by Floyd Bloom in 1977), and adjunct professor in psychiatry at UCSD.

## Director of the National Institute on Alcohol Abuse and Alcoholism, 2014–present

When T. K. Li retired as director of NIAAA, a five-year debate ensued to merge NIAAA with NIDA while acting director, Ken Warren, guided NIAAA. Ultimately, this merger failed, largely because of a lack of enthusiasm of all parties and the enormous effort and disruption such a merger would cause in the field. As a result, in 2013, the National Institutes of Health (NIH) began a search to recruit a new director of NIAAA. I was urged to apply by many of my colleagues and friends, notably by Nora Volkow, Director of NIDA, with whom I had been collaborating in writing and scientific discussion for many years. I was offered the position. After much discussion, I realized that this was a prime opportunity to move the field forward and possibly move the field in directions that in my opinion were long neglected. Notable among these were the lack of emphasis on alcohol as a drug of addiction when considering its enormous burden on society, the lack

of a heuristic framework for studying the role of motivational withdrawal (hyperkatifeia) in driving AUD and substance use disorder in general, the conceptual gap between clinical studies and preclinical work on which my collaboration with Barbara Mason had shone a light, and the lack of translation of evidence-based information about alcohol to the public.

During my tenure as Director of NIAAA, I can list many accomplishments, including the current organization of the institute; its direction; its major mission of generating evidence-based information about the etiology of AUD, including its diagnosis, prevention, and treatment; and the dissemination of this information to the public.

For the organization of NIAAA, I developed and implemented a vision for the institute that effectively included providing a positive environment for the exchange of ideas by including my leadership team and entire staff in decisions. I streamlined the office of the Director and shared all decision making with my deputy (Patricia Powell), executive officer (Vicki Buckley), and Associate Director for Basic Research (Bridget Williams-Simmons), which because of each of our unique skills and backgrounds, strengthened our approach to leadership. We also welcomed regular input from my intramural scientific director (George Kunos) and clinical director (David Goldman) and division directors (Antonio Noronha, Ralph Hingson, Kathy Jung, and Raye Litten), and senior adviser to the director (Aaron White). These individuals and many others became what for me is our NIAAA family, and all that follows was the result of our efforts together as a team.

In the Intramural Research Program, I dissolved the large laboratory structure and employed an academic structure in which each investigator directed their own independent laboratory. I also complied with the overall NIH guidance to have the clinical director report directly to me. As a result, our outstanding NIAAA Intramural Research Program has become an incubator for innovative basic, translational, and clinical alcohol research and training.

Given that alcohol misuse contributes to more than 200 diseases and disorders, I made collaborations across NIH institutes/centers and throughout the federal government a priority. NIAAA maintains a very active Collaboration on Research on Addiction (CRAN) with NIDA and the National Cancer Institute (NCI). One of the most notable accomplishments of CRAN was the development and continued success of the Adolescent Brain Cognitive Development (ABCD) study, which is following the development of more than 10,000 children from nine to ten years old to adulthood, conducting every-other-year brain imaging and yearly neuropsychological testing and other environmental measures (Volkow et al., 2018). The ABCD study benefited significantly from the National Consortium on Alcohol and Neurodevelopment in Adolescence study launched by NIAAA in 2012. The ABCD data are available to researchers through the National Institute of Mental Health data archive and will provide a rich set of data on normal adolescent development of inestimable value for future research. NIAAA

staff remain actively involved in planning and cosponsoring programs with other NIH institutes that are associated with pain, fetal alcohol spectrum disorder, child development, basic neuroscience (the BRAIN initiative), liver disease, cancer, and SARS-CoV-2.

As NIH sought to increase diversity and inclusion in the workforce and support research on health disparities, I rallied NIAAA staff at multiple levels to address these issues in meaningful ways with actionable steps, including an emphasis on hiring women to close the male–female gap in senior positions. I also strongly supported NIAAA’s Intramural Research Program in recruiting highly talented underrepresented minority investigators into tenure-track positions. I have led efforts to improve the culture and expand the health disparities portfolio, and I established an NIAAA Advisory Council working group on mentoring underrepresented minorities. I also continued to foster the next generation of alcohol researchers by promoting training through career development awards, strongly supporting early-stage investigators through funding and outreach, and developing multiple avenues for mentorship.

Throughout my tenure at NIAAA, I have developed not only a conceptual neurobiological framework to guide studies of the neurobiology of AUD that has proven to have invaluable heuristic utility but also a research translation framework for NIAAA to convey its evidence-based research to the real world. This research translation framework has resulted in a number of direct web-based programs to inform the public about alcohol misuse and key conceptual framework papers and reviews on such topics as the brain disorder model of addiction (Volkow and Koob, 2015); development of an Addictions Neuroclinical Assessment Framework (Kwako et al., 2016); microcircuitry analysis of the neurobiology of addiction (Koob and Volkow, 2016); a review of the state of knowledge of the molecular site of action for the initiation of alcohol effects on the brain (Cui and Koob, 2017); validation of the three domains of dysfunction that correspond to the three-stage cycle of addiction (Kwako et al., 2019); a major review on alcohol and sleep (Koob and Colrain, 2020); a commentary on the interaction between alcohol misuse, hyperkatifeia, the SARS-CoV-2 pandemic, and deaths of despair (Koob et al., 2020b); and a review with both the NIDA and National Institute of Mental Health Directors on choosing appropriate language to reduce stigma in the fields of addiction and mental health in general (Volkow et al., 2021).

With regard to informing the public, I supported and initiated major efforts to increase awareness of the consequences of alcohol misuse, including AUD, to all facets of the community. I fully supported and helped with the rollout of College Alcohol Intervention Matrix (College AIM), an evidence-based menu of prevention options for college and university students. Started before my arrival at NIAAA, College AIM rates both individual and community prevention programs by effectiveness and cost. Under my tenure, it

has been distributed to every college and university in the United States. In addition, in 2016, NIAAA collaborated with the television network HBO to produce a landmark documentary called *Risky Drinking*, which charts the spectrum of AUD across four human vignettes in the context of AUD as a brain disorder and in the context of treatment options.

I then initiated the NIAAA Alcohol Treatment Navigator, a clinical core resource, efforts to operationally define recovery, efforts to develop a consensus definition of fetal alcohol spectrum disorder, efforts to facilitate concurrent treatment of AUD with alcohol-associated liver disease, and efforts to compile a prevention core resource for adolescents. For example, the Alcohol Treatment Navigator provides key information about how AUD is a spectrum disorder with a corresponding range of treatments and two locators whereby one can enter a zip code and find a treatment provider in that zip code area. Subsequently, we added a portal to assist healthcare providers in making effective referrals for treatment.

I also initiated and led the development of a Healthcare Professional's Core Resource released in 2022 that provides key information to healthcare providers, including physicians, pharmacists, psychologists, and nurse practitioners, about alcohol and treatment options. Input from clinicians, researchers, and other stakeholders has produced an accurate, extensive resource for what all healthcare providers who interface with patients need to know about alcohol's effects on the human body across the lifespan. An outreach plan to maximize the impact of this critical resource is underway. Our outreach efforts through our website, Rethinking Drinking, College Aim, and the NIAAA Navigator have been updated to meet the challenges of the COVID-19 pandemic and new advances.

We also have made significant strides engaging clinicians and other healthcare providers to factor in a patient's alcohol consumption in their overall healthcare. My efforts to engage specialists in liver disease through clinical researchers and the American Association of Liver Disease is also transforming healthcare by increasing the concurrent treatment of alcohol-associated liver disease and AUD. I also shifted priorities in the NIAAA portfolio toward research on the older adult population and women in response to epidemiological studies that show an increase in alcohol use, binge drinking, and consequences in these subpopulations. Collectively, these efforts highlight our efforts at understanding the changing needs of the U.S. population and ability to nimbly shift priorities as necessary to maximize program efficiency and results.

Finally, under my leadership, NIAAA expanded its research portfolio and maintained a robust, high-quality research program despite the challenges of SARS-CoV-2, which necessitated adapting to new research priorities and opportunities. Although considerable staff time was devoted to pandemic-related activities, I ensured that priorities to synergize research efforts and

disseminate information to the public advanced with vigor. Examples include integrating pain, opioid use disorder, and sleep measures with AUD in clinical studies; supporting pharmacotherapy clinical trials for alcohol-related liver disease and AUD; finalizing the Healthcare Professional's Core Resource; implementing a definition of AUD recovery for research; initiating a registry to follow patients who received AUD treatment; boosting research on fetal alcohol spectrum disorder prevention and treatment; and increasing focus on reducing stigma. Of all of our tangible efforts at NIAAA during my tenure, I am most proud of the *Risky Drinking* documentary, College Aim, Rethinking Drinking, the NIAAA Treatment Navigator, development of an operational definition of recovery, and the Healthcare Professional's Core Resource.

### National Institute on Drug Abuse, Intramural Research Program, 2014–present

Upon arriving at NIH in 2014, I was allowed to continue supervising my research group at TSRI for two years while transitioning all my trainees to their next career goals. At the same time, I won an appointment as a tenured senior investigator in the NIDA Intramural Research Program where I established a basic research laboratory called the Neurobiology of Addiction Section in the Integrative Neuroscience Research Branch at the Bayview Center in Baltimore. I immediately recruited Leandro Vendruscolo, a senior postdoctoral fellow from my laboratory at TSRI, to coordinate my laboratory at NIDA. Brooke Schmeichel, who had just begun her fellowship with me at TSRI, also made the transition to NIDA. I then began a new group that consists of three to four postdoctoral fellows at any given time, up to six post-baccalaureate fellows, and currently two PhD students. My role gradually is evolving into what I call a “Le Pere Koob” role (“the father Koob” role), in which I help direct the overall program of the laboratory, participate in all the experimental designs, and help guide postdoctoral fellows toward K99 grant awards or faculty positions and postbaccalaureate fellows toward graduate or medical school.<sup>4</sup>

Some of the main accomplishments include the continued development of new animal models of “endophenotypes” that are associated with addiction, with a focus on negative emotional states that are associated with the withdrawal and negative affect stage of the addiction cycle, including the vapor-induced escalation of drug intake in rats (Vendruscolo et al., 2018), escalation of intravenous self-administration in mice (Towers et al.,

<sup>4</sup>(2014–2021) Predoctoral fellows: Kay Nisbett, Rani Richardson. Postdoctoral fellows: Stephanie Carmack, Mandy McCracken, Brendan Tunstall, Emily Lowery-Gionta, Renata Marchette, Caroline Pantazis, M. Adrienne McGinn, Nadia Said. K99 awardees: Emily Lowery-Gionta, Brooke Schmeichel, Brendan Tunstall, Khaled Moussawi.

2019), vapor escalation in mice (Moussawi et al., 2020), and pain measures (Marchette et al., 2021). We also identified and focused on exploring the neurocircuitry that is mediated by three neurochemical systems that are involved in the negative emotional state that drives the withdrawal and negative affect stage, including CRF, glucocorticoids, and mineralocorticoids (de Guglielmo et al., 2019; Vendruscolo et al., 2015; Aoun et al., 2018); dynorphin/ $\kappa$ -opioid systems (Marchette et al., 2021); and oxytocin (Tunstall et al., 2019).

To extend our neurocircuitry approach to protracted withdrawal, with implications for the etiology of craving and relapse, functional magnetic resonance imaging (fMRI) was applied in rats to identify amygdala and hypothalamic neurocircuits that were activated by stimuli that were previously paired with heroin withdrawal. This activation was related to the degree of heroin dependence, supporting the significance of conditioned negative affect in sustaining compulsive-like heroin seeking and taking (Carmack et al., 2019). These results were consistent with earlier observations in collaboration with Barry Everitt and Gery Schulteis, in which conditioned withdrawal (conditioned suppression of responding on a fixed-ratio schedule for food) could be blocked by lesions of the basolateral amygdala (Schulteis et al., 2000). In a follow-up imaging study, a putative rat salience network was identified using modularity analysis on resting-state fMRI data from rats to parcellate the rat insula into functional subdivisions, and mouse tract tracing data from the Allen Brain Atlas was used to confirm the network's underlying structural connectivity. From the data from animals in the Carmack et al. (2019) study, a salience network, which consisted primarily of the ventral anterior insula and anterior cingulate cortex, responded to conditioned cues and showed greater functional connectivity to the default mode network during conditioned heroin withdrawal (Tsai et al., 2020). These results suggest that the insula and salience network may serve as markers of highly salient environmental stimuli, particularly conditioned stimuli paired with heroin withdrawal.

During the SARS-CoV-2 pandemic shutdown in 2020–2021, my collaborators and I wrote several reviews that have refined a conceptual framework that focuses on the role of negative emotional states in the withdrawal/negative affect stage of the addiction cycle. Noteworthy reviews included alcohol tolerance (Elvig et al., 2021); allostasis theory in opioid tolerance (Ballantyne and Koob, 2021); cues conditioned to withdrawal and negative reinforcement (Pantazis et al., 2021); opponent process, hyperkatifeia, negative reinforcement, and opioid addiction (Koob, 2020; Koob, 2021); using neuroimaging for the assessment of AUD (Voon et al., 2020); tolerance to opioids and allostasis theory (Ballantyne and Koob, 2021); and neurocircuitry of the comorbid posttraumatic stress disorder-opioid use disorder state (Upadhyay et al., 2021). To date, I have mentored or comentored 13 PhD students, 84 postdoctoral fellows, and 11 K99 grant awardees.



## Summary

My journey in research has always been predicated on trying to understand the neurobiological mechanisms of the hedonic components of motivation: reward and anti-reward. After spending the first half of my career understanding how we feel good, I have spent the remainder of my career trying to understand how we feel bad. My studies on the neurobiology of stress and the neurobiology of addiction have come full circle and have provided windows on how the brain processes such emotions and how such processes go awry. I would like to think that our efforts have contributed to considering hyperkatifeia as a driving force of negative reinforcement in addiction and have provided insights into how we feel and express negative emotions in general. I have been blessed with wonderful mentors, students, postdoctoral fellows, collaborators, and staff, all of whom have enriched my journey, and I want to thank them all. Perhaps most poignantly as my career winds down, I am grateful for the opportunities I have had at NIAAA and in my writing to disseminate evidence-based science, particularly evidence-based neuroscience, to the public. Hopefully, our efforts in this regard will be our legacy of helping humankind in its never-ending quest for hedonic homeostasis.

## Selected Bibliography

- Ahmed SH, Kenny PJ, Koob GF, Markou A (2002) Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. *Nat Neurosci* 5: 625–6.
- Ahmed SH, Koob GF (1998) Transition from moderate to excessive drug intake: change in hedonic set point. *Science* 282: 298–300.
- American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. American Psychiatric Press, Washington DC.
- Anlezark GM, Crow TJ, Greenway AP (1973) Impaired learning and decreased cortical norepinephrine after bilateral locus coeruleus lesions. *Science* 181: 682–4.
- Aoun EG, Jimenez VA, Vendruscolo LF, Walter NAR, Barbier E, Ferrulli A, Haass-Koffler CL, Darakjian P, Lee MR, Addolorato G, Heilig M, Hitzemann R, Koob GF, Grant KA, Leggio L (2018) A relationship between the aldosterone-mineralocorticoid receptor pathway and alcohol drinking: preliminary translational findings across rats, monkeys and humans. *Mol Psychiatry* 23: 1466–73.
- Ballantyne JC, Koob GF (2021) Allostasis theory in opioid tolerance. *Pain* 162: 2315–9.
- Baldwin HA, Rassnick S, Rivier J, Koob GF, Britton KT (1991) CRF antagonist reverses the "anxiogenic" response to ethanol withdrawal in the rat. *Psychopharmacology* 103: 227–32.
- Baumeister RF, Heatherton TF, Tice DM (1994) *Losing Control: How and Why People Fail at Self-Regulation*. Academic Press, San Diego.
- Blednov YA, Ponomarev I, Geil C, Bergeson S, Koob GF, Harris RA (2011) Neuroimmune regulation of alcohol consumption: behavioral validation of genes obtained from genomic studies. *Addict Biol* 17: 108–20.

- Brady JV (1956) Assessment of drug effects on emotional behavior. *Science* 123: 1033–4.
- Breese GR, Overstreet DH, Knapp DJ, Navarro M (2005) Prior multiple ethanol withdrawals enhance stress-induced anxiety-like behavior: inhibition by CRF1- and benzodiazepine-receptor antagonists and a 5-HT<sub>1a</sub>-receptor agonist. *Neuropsychopharmacology* 30: 1662–9.
- Britton KT, Lee G, Koob GF (1988) Corticotropin releasing factor and amphetamine exaggerate partial agonist properties of benzodiazepine antagonist Ro 15-1788 in the conflict test. *Psychopharmacology* 94: 306–11.
- Brown MR, Fisher LA, Rivier J, Spiess J, Rivier C, Vale W (1982) Corticotropin-releasing factor: effects on the sympathetic nervous system and oxygen consumption. *Life Sci* 30: 207–10.
- Carmack SA, Keeley RJ, Vendruscolo JCM, Lowery-Gionta EG, Lu H, Koob GF, Stein EA, Vendruscolo LF (2019) Heroin addiction engages negative emotional learning brain circuits in rats. *J Clin Invest* 130: 2480–4.
- Chen SA, O'Dell L, Hoefer M, Greenwell TN, Zorrilla EP, Koob GF (2006) Unlimited access to heroin self-administration: independent motivational markers of opiate dependence. *Neuropsychopharmacology* 31: 2692–707 [corrigendum: 31:2802].
- Chu K, Koob GF, Cole M, Zorrilla EP, Roberts AJ (2007) Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF1 receptor antagonist antalarmin and by CRF1 receptor knockout. *Pharmacol Biochem Behav* 86: 813–21.
- Cohen A, Koob GF, George O (2012) Robust escalation of nicotine intake with extended access to nicotine self-administration and intermittent periods of abstinence. *Neuropsychopharmacology* 37: 2153–60.
- Cottone P, Sabino V, Roberto M, Bajo M, Pockros L, Frihauf JB, Fekete EM, Steardo L, Rice KC, Grigoriadis DE, Conti B, Koob GF, Zorrilla EP (2009) CRF system recruitment mediates dark side of compulsive eating. *Proc Natl Acad Sci USA* 106: 20016–20.
- Crow TJ (1973) Catecholamine-containing neurones and electrical self-stimulation: 2. A theoretical interpretation and some psychiatric implications. *Psychol Med* 3: 66–73.
- Cui C, Koob GF (2017) Titrating tipsy targets: the neurobiology of low-dose alcohol. *Trends Pharmacol Sci* 38: 556–68.
- de Guglielmo G, Kallupi M, Pomrenze M, Crawford E, Simpson S, Schweitzer P, Koob GF, Messing RO, George O (2019) Inactivation of a CRF-dependent amygdalofugal pathway reverses addiction-like behaviors in alcohol-dependent rats. *Nat Commun* 10: 1238.
- de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS 2nd, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA* 95: 322–7.
- De Wied D (1976) Behavioral effects of intraventricularly administered vasopressin and vasopressin fragments. *Life Sci* 46: 27–9.

- de Witte P, Littleton J, Parot P, Koob G (2005) Neuroprotective and abstinence-promoting effects of acamprostate: elucidating the mechanism of action. *CNS Drugs* 19: 517–37.
- Edwards S, Koob GF (2013) Escalation of drug self-administration as a hallmark of persistent addiction liability. *Behav Pharmacol* 24: 356–62.
- Ettenberg A, Pettit HO, Bloom FE, Koob GF (1982) Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. *Psychopharmacology* 78: 204–9.
- Elvig SK, McGinn A, Smith C, Arends MA, Koob GF, Vendruscolo LF (2021) Tolerance to alcohol: a critical yet understudied factor in alcohol addiction. *Pharmacol Biochem Behav* 204: 173155.
- Everitt BJ, Wolf ME (2002) Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci* 22: 3312–20 [erratum: 22(16): 1a].
- Ferster CB, Skinner BF (1957) *Schedules of Reinforcement*. Appleton-Century-Crofts, New York.
- Funk CK, O'Dell LE, Crawford EF, Koob GF (2006) Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. *J Neurosci* 26: 11324–32.
- Funk CK, Zorrilla EP, Lee MJ, Rice KC, Koob GF (2007) Corticotropin-releasing factor 1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. *Biol Psychiatry* 61: 78–86.
- Gantt WH (1942) The origin and development of nervous disturbances experimentally produced. *Am J Psychiatry* 98: 475–81.
- Gehlert DR, Cippitelli A, Thorsell A, Le AD, Hipskind PA, Hamdouchi C, Lu J, Hembre EJ, Cramer J, Song M, McKinzie D, Morin M, Ciccocioppo R, Heilig M (2007) 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism. *J Neurosci* 27: 2718–26.
- George O, Ghozland S, Azar MR, Cottone P, Zorrilla EP, Parsons LH, O'Dell LE, Richardson HN, Koob GF (2007) CRF-CRF<sub>1</sub> system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. *Proc Natl Acad Sci USA* 104: 17198–203.
- George O, Koob GF, Vendruscolo LF (2014) Negative reinforcement via motivational withdrawal is the driving force behind the transition to addiction. *Psychopharmacology* 231: 3911e7.
- Greenwell TN, Funk CK, Cottone P, Richardson HN, Chen SA, Rice K, Zorrilla EP, Koob GF (2009) Corticotropin-releasing factor-1 receptor antagonists decrease heroin self-administration in long-, but not short-access rats. *Addict Biol* 14: 130–43.
- Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B, Maffrand JP, Soubrie P (2002) Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proc Natl Acad Sci USA* 99: 6370–5.

- Grieder TE, Herman MA, Contet C, Tan LA, Vargas-Perez H, Cohen A, Chwalek M, Maal-Bared G, Freiling J, Schlosburg JE, Clarke L, Crawford E, Koebel P, Repunte-Cononigo V, Sanna PP, Tapper AR, Roberto M, Kieffer BL, Sawchenko PE, Koob GF, van der Kooy D, George O (2014) VTA CRF neurons mediate the aversive effects of nicotine withdrawal and promote intake escalation. *Nat Neurosci* 17: 1751–8.
- Harris RA, Koob GF (2017) The future is now: a 2020 view of alcoholism research. *Neuropharmacology* 122: 1–2.
- Heilig M, McLeod S, Koob GK [sic], Britton KT (1992) Anxiolytic-like effect of neuropeptide Y (NPY), but not other peptides in an operant conflict test. *Regul Pept* 41: 61–9.
- Heinrichs SC, Cole BJ, Merlo-Pich E, Menzaghi F, Koob GF, Hauger RL (1992) Endogenous corticotropin-releasing factor modulates feeding induced by neuropeptide Y or a tail-pinch stressor. *Peptides* 13: 879–4.
- Heyser CJ, Roberts AJ, Schulteis G, Koob GF (1999) Central administration of an opiate antagonist decreases oral ethanol self-administration in rats. *Alcohol Clin Exp Res* 23: 1468–76.
- Hoffman HS, Ratner AM, Eisener LA (1972) Role of visual imprinting in the emergence of specific filial attachments in ducklings. *J Comp Physiol Psychol* 81: 399–409.
- Hubner CB, Koob GF (1990) The ventral pallidum plays a role in mediating cocaine and heroin self-administration in the rat. *Brain Res* 508: 20–9.
- Jang CG, Whitfield T, Schulteis G, Koob GF, Wee S (2013) A dysphoric-like state during early withdrawal from extended access to methamphetamine self-administration in rats. *Psychopharmacology* 225: 753–63.
- Kenny PJ, Chen SA, Kitamura O, Markou A, Koob GF (2006) Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. *J Neurosci* 26: 5894–900.
- Kitamura O, Wee S, Specio SE, Koob GF, Pulvirenti L (2006) Escalation of methamphetamine self-administration in rats: a dose-effect function. *Psychopharmacology* 186: 48–53.
- Koob GF (1982) The dopamine anhedonia hypothesis: a pharmacological phrenology. *Behav Brain Sci* 5: 63–4.
- Koob GF (1992) Dopamine, addiction and reward. *Semin Neurosci* 4: 139–48.
- Koob GF (2017) The dark side of addiction: the Horsley Gantt to Joseph Brady connection. *J Nerv Ment Dis* 205: 270–2.
- Koob GF (2020) Neurobiology of opioid addiction: opponent process, hyperkatifeia and negative reinforcement. *Biol Psychiatry* 87: 44–53.
- Koob GF (2021) Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. *Pharmacol Rev* 73: 163–201.
- Koob GF, Annau Z (1973) Effect of hypoxia on hypothalamic mechanisms. *Am J Physiol* 224: 1403–8.
- Koob GF, Annau Z (1974) Behavioral and neurochemical alterations induced by hypoxia in rats. *Am J Physiol* 227: 73–8.
- Koob GF, Annau Z, Blake WD Jr, Weinstein SA (1970) Hypothalamic self-stimulation, eating, and drinking: the effects of hypoxia. *Commun Behav Biol A* 5: 205–10.

- Koob GF, Arends MA, Le Moal M (2014) *Drugs, Addiction, and the Brain*. Academic Press, San Diego.
- Koob GF, Arends MA, McCracken M, Le Moal M (2019) *Neurobiology of Addiction: Volume 1. Introduction to Addiction*. Elsevier, New York.
- Koob GF, Arends MA, McCracken M, Le Moal M (2020a) *Neurobiology of Addiction: Volume 2. Psychostimulants*. Elsevier, New York.
- Koob GF, Arends MA, McCracken M, Le Moal M (2021) *Neurobiology of Addiction: Volume 3. Alcohol*. Elsevier, New York.
- Koob GF, Balcom GJ, Meyerhoff JL (1975) Dopamine and norepinephrine levels in the nucleus accumbens, olfactory tubercle, and corpus striatum following lesions in the ventral tegmental area. *Brain Res* 94: 45–55.
- Koob GF, Bloom FE (1988) Cellular and molecular mechanisms of drug dependence. *Science* 242: 715–23.
- Koob GF, Colrain IM (2020) Alcohol use disorder and sleep disturbances: a feed-forward allostatic framework. *Neuropsychopharmacology* 45: 141–65.
- Koob GF, Everitt BJ, Robbins TW (2008) Reward, motivation, and addiction. In: Squire LG, Berg D, Bloom FE, Du Lac S, Ghosh A, Spitzer N (eds) *Fundamental Neuroscience*, 3rd edition. Academic Press, Amsterdam, pp. 987–1016.
- Koob GF, Fray PJ, Iversen SD (1976) Tail-pinch stimulation: sufficient motivation for learning. *Science* 194: 637–9.
- Koob GF, Fray PJ, Iversen SD (1978a) Self-stimulation at the lateral hypothalamus and locus coeruleus after specific unilateral lesions of the dopamine system. *Brain Res* 146: 123–40.
- Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. *Science* 278: 52–8.
- Koob GF, Le Moal M (2005) Plasticity of reward neurocircuitry and the “dark side” of drug addiction. *Nat Neurosci* 8: 1442–4.
- Koob GF, Le Moal M (2006) *Neurobiology of Addiction*. Academic Press, London.
- Koob GF, Le Moal M (2008) Addiction and the brain antireward system. *Annu Rev Psychol* 59: 29–53.
- Koob GF, Lloyd GK, Mason BJ (2009) Development of pharmacotherapies for drug addiction: a Rosetta Stone approach. *Nat Rev Drug Discov* 8: 500–15.
- Koob GF, Mason BJ (2016) Existing and future drugs for the treatment of the dark side of addiction. *Annu Rev Pharmacol Toxicol* 56: 299–322.
- Koob GF, Powell P, White A (2020b) Addiction as a coping response: hyperkatifeia, deaths of despair, and COVID-19. *Am J Psychiatry* 177: 1031–7.
- Koob GF, Riley SJ, Smith SC, Robbins TW (1978b) Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity and amphetamine anorexia in the rat. *J Comp Physiol Psychol* 92: 917–27.
- Koob GF, Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacol Rev* 35: 217–38 [erratum: 35:1051].
- Koob GF, Volkow ND (2016) Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3: 760–73.
- Koob GF, Wall TL, Bloom FE (1989) Nucleus accumbens as a substrate for the aversive stimulus effects of opiate withdrawal. *Psychopharmacology* 98: 530–4.

- Koob GF, Weiss F (1990) Pharmacology of drug self-administration. *Alcohol* 7: 193–7.
- Kwako LE, Momenan R, Litten RZ, Koob GF, Goldman D (2016) Addictions neuro-clinical assessment: a neuroscience-based framework for addictive disorders. *Biol Psychiatry* 80: 179–89.
- Kwako LE, Schwandt ML, Ramchandani VA, Diazgranados N, Koob GF, Volkow ND, Blanco C, Goldman D (2019) Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *Am J Psychiatry* 176: 744–53.
- Lai C, Brow MA, Nave KA, Noronha AB, Quarles RH, Bloom FE, Milner RJ, Sutcliffe JG (1987) Two forms of 1B236/myelin-associated glycoprotein, a cell adhesion molecule for postnatal neural development, are produced by alternative splicing. *Proc Natl Acad Sci USA* 84: 4337–41.
- Lebrun C, Le Moal M, Koob GF, Bloom FE (1985) Vasopressin pressor antagonist injected centrally reverses behavioral effects of peripheral injection of vasopressin, but only at doses that reverse increase in blood pressure. *Regul Pept* 11: 173–81.
- Le Moal M, Dantzer R, Michaud B, Koob GF (1987) Centrally injected arginine vasopressin (AVP) facilitates social memory in rats. *Neurosci Lett* 77: 353–9.
- Le Moal M, Dantzer R, Mormede P, Baduel A, Lebrun C, Ettenberg A, van der Kooy D, Wenger J, Deyo S, Koob GF, Bloom FE (1984) Behavioral effects of peripheral administration of arginine vasopressin: a review of our search for a mode of action and a hypothesis. *Psychoneuroendocrinology* 9: 319–41.
- Le Moal M, Koob GF, Koda LY, Bloom FE, Manning M, Sawyer WH, Rivier J (1981) Vasopressor receptor antagonist prevents behavioural effects of vasopressin. *Nature* 291: 491–3.
- Marchette RCN, Gregory-Flores A, Tunstall BJ, Carlson ER, Jackson S, Sulima A, Rice KC, Koob GF, Vendruscolo LF (2021)  $\kappa$ -Opioid receptor antagonism reverses heroin withdrawal-induced hyperalgesia in male and female rats. *Neurobiol Stress* 14: 100325.
- Mason BJ, Goodman AM, Chabac S, Lehert P (2006) Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. *J Psychiatr Res* 40: 383–93.
- Mason BJ, Light JM, Escher T, Drobos DJ (2008) Effect of positive and negative affective stimuli and beverage cues on measures of craving in non treatment-seeking alcoholics. *Psychopharmacology* 200: 141–50.
- Mason BJ, Light JM, Williams LD, Drobos DJ (2009) Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol* 14: 73–83.
- Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A (2014) Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med* 174: 70–7.
- Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB (1999) A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 56: 719–24.
- Pantazis CB, Gonzalez LA, Tunstall BJ, Carmack SA, Koob GF, Vendruscolo LF (2021) Cues conditioned to withdrawal and negative reinforcement: neglected but key motivational elements driving opioid addiction. *Sci Adv* 7: eabf0364.

- Merlo-Pich E, Lorang M, Yeganeh M, Rodriguez de Fonseca F, Raber J, Koob GF, Weiss F (1995) Increase of extracellular corticotropin-releasing factor-like immunoreactivity levels in the amygdala of awake rats during restraint stress and ethanol withdrawal as measured by microdialysis. *J Neurosci* 15: 5439–47.
- Montigny R, Kahn O (1977) *Cuisine Sans Souci*. Le-Livre, Sablons.
- Moussawi K, Ortiz MM, Gantz SC, Tunstall BJ, Marchette RCN, Bonci A, Koob GF, Vendruscolo LF (2020) Fentanyl vapor self-administration model in mice to study opioid addiction. *Sci Adv* 6: eabc0413.
- Mulligan MK, Ponomarev I, Hitzemann RJ, Belknap JK, Tabakoff B, Harris RA, Crabbe JC, Blednov YA, Grahame NJ, Phillips TJ, Finn DA, Hoffman PL, Iyer VR, Koob GF, Bergeson SE (2006) Toward understanding the genetics of alcohol drinking through transcriptome meta-analysis. *Proc Natl Acad Sci USA* 103: 6368–73.
- Olds J, Milner P (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 47: 419–27.
- Olive MF, Koenig HN, Nannini MA, Hodge CW (2002) Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. *Pharmacol Biochem Behav* 72: 213–20.
- Park PE, Schlosburg JE, Vendruscolo LF, Schulteis G, Edwards S, Koob GF (2015) Chronic CRF<sub>1</sub> receptor blockade reduces heroin intake escalation and dependence-induced hyperalgesia. *Addict Biol* 20: 275–84.
- Pettit HO, Ettenberg A, Bloom FE, Koob GF (1984) Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. *Psychopharmacology* 84: 167–73.
- Pollard GT, Howard JL (1979) The Geller-Seifter conflict paradigm with incremental shock. *Psychopharmacology* 62: 117–21.
- Rassnick S, Heinrichs SC, Britton KT, Koob GF (1993) Microinjection of a corticotropin-releasing factor antagonist into the central nucleus of the amygdala reverses anxiogenic-like effects of ethanol withdrawal. *Brain Res* 605: 25–32.
- Rassnick S, Pulvirenti L, Koob GF (1992) Oral ethanol self-administration in rats is reduced by the administration of dopamine and glutamate receptor antagonists into the nucleus accumbens. *Psychopharmacology* 109: 92–8.
- Rhodes JS, Best K, Belknap JK, Finn DA, Crabbe JC (2005) Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. *Physiol Behav* 84: 53–63.
- Richter RM, Weiss F (1999) In vivo CRF release in rat amygdala is increased during cocaine withdrawal in self-administering rats. *Synapse* 32: 254–61.
- Roberts DCS, Koob GF, Klonoff P, Fibiger HC (1980) Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacol Biochem Behav* 12: 781–7.
- Roberts AJ, Heyser CJ, Cole M, Griffin P, Koob GF (2000) Excessive ethanol drinking following a history of dependence: animal model of allostasis. *Neuropsychopharmacology* 22: 581–94.
- Robbins TW, Koob GF (1980) Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. *Nature* 285: 409–12.

- Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev* 18: 247–91.
- Robledo P, Koob GF (1993) Two discrete nucleus accumbens projection areas differentially mediate cocaine self-administration in the rat. *Behav Brain Res* 55: 159–66.
- Rodriguez de Fonseca F, Carrera MRA, Navarro M, Koob GF, Weiss F (1997) Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science* 276: 2050–4.
- Samson HH (1986) Initiation of ethanol reinforcement using a sucrose-substitution procedure in food- and water-sated rats. *Alcohol Clin Exp Res* 10: 436–42.
- Schulteis G, Ahmed SH, Morse AC, Koob GF, Everitt BJ (2000) Conditioning and opiate withdrawal: the amygdala links neutral stimuli with the agony of overcoming drug addiction. *Nature* 405: 1013–4.
- Schulteis G, Heyser CJ, Koob GF (1997) Opiate withdrawal signs precipitated by naloxone following a single exposure to morphine: potentiation with a second morphine treatment. *Psychopharmacology* 129: 56–65.
- Schulteis G, Markou A, Gold LH, Stinus L, Koob GF (1994) Relative sensitivity to naloxone of multiple indices of opiate withdrawal: a quantitative dose-response analysis. *J Pharmacol Exp Ther* 271: 1391–8.
- Sessions GR, Kant GJ, Koob GF (1976) Locus coeruleus lesions and learning in the rat. *Physiol Behav* 17: 853–9.
- Shurman J, Koob GF, Gutstein HB (2010) Opioids, pain, the brain, and hyperkatifeia: a framework for the rational use of opioids for pain. *Pain Med* 11: 1092–8.
- Solomon RL (1980) The opponent-process theory of acquired motivation: the costs of pleasure and the benefits of pain. *Am Psychologist* 35: 691–712.
- Solomon RL, Corbit JD (1974) An opponent-process theory of motivation: 1. Temporal dynamics of affect. *Psychol Rev* 81: 119–45.
- Sommer WH, Rimondini R, Hansson AC, Hipskind PA, Gehlert DR, Barr CS, Heilig MA (2008) Upregulation of voluntary alcohol intake, behavioral sensitivity to stress, and amygdala *Crhr1* expression following a history of dependence. *Biol Psychiatry* 63: 139–45.
- Specio SE, Wee S, O'Dell LE, Boutrel B, Zorrilla EP, Koob GF (2008) CRF<sub>1</sub> receptor antagonists attenuate escalated cocaine self-administration in rats. *Psychopharmacology* 196: 473–82.
- Stinus L, Koob GF, Ling N, Bloom FE, Le Moal M (1980) Locomotor activation induced by infusion of endorphins into the ventral tegmental area: evidence for opiate-dopamine interactions. *Proc Natl Acad Sci USA* 77: 2323–7.
- Stinus L, Caille S, Koob GF (2000) Opiate withdrawal-induced place aversion lasts for up to 16 weeks. *Psychopharmacology* 149: 115–20.
- Stinus L, Cador M, Zorrilla EP, Koob GF (2005) Buprenorphine and a CRF<sub>1</sub> antagonist block the acquisition of opiate withdrawal-induced conditioned place aversion in rats. *Neuropsychopharmacology* 30: 90–8.
- Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W (1982) Corticotropin releasing factor produces behavioural activation in rats. *Nature* 297: 331–3.



- Swerdlow NR, Britton KT, Koob GF (1989) Potentiation of acoustic startle by corticotropin-releasing factor (CRF) and by fear are both reversed by  $\gamma$ -helical CRF (9-41). *Neuropsychopharmacology* 2: 285–92.
- Towers EB, Tunstall BJ, McCracken MM, Vendruscolo LF, Koob GF (2019) Male and female mice develop escalation of heroin intake and dependence following extended access. *Neuropharmacology* 151: 189–94.
- Tazi A, Dantzer R, Le Moal M, Rivier J, Vale W, Koob GF (1987) Corticotropin-releasing factor antagonist blocks stress-induced fighting in rats. *Regul Pept* 18: 37–42.
- Thatcher-Britton K, Koob GF (1986) Alcohol reverses the proconflict effect of corticotropin-releasing factor. *Regul Pept* 16: 315–20.
- Tsai PJ, Keeley RJ, Carmack SA, Vendruscolo JCM, Lu H, Gu H, Vendruscolo LF, Koob GF, Lin CP, Stein EA, Yang Y (2020) Converging structural and functional evidence for a rat salience network. *Biol Psychiatry* 88: 867–78.
- Tunstall BJ, Kirson D, Zallar LJ, McConnell SA, Vendruscolo JCM, Ho CP, Oleata CS, Khom S, Manning M, Lee MR, Leggio L, Koob GF, Roberto M, Vendruscolo LF (2019) Oxytocin blocks enhanced motivation for alcohol in alcohol dependence and blocks alcohol effects on GABAergic transmission in the central amygdala. *PLoS Biol* 17: e20066421.
- Upadhyay J, Verrico CD, Cay M, Kodel S, Yammine L, Koob GF, Schreiber R (2021) Neurocircuitry basis of the OUD-PTSD comorbid state: conceptual analyses using a dimensional framework. *Lancet Psychiatry*, in press.
- Valdez GR, Roberts AJ, Chan K, Davis H, Brennan M, Zorrilla EP, Koob GF (2002) Increased ethanol self-administration and anxiety-like behavior during acute withdrawal and protracted abstinence: regulation by corticotropin-releasing factor. *Alcohol Clin Exp Res* 26: 1494–501.
- Valdez GR, Zorrilla EP, Roberts AJ, Koob GF (2003) Antagonism of corticotropin-releasing factor attenuates the enhanced responsiveness to stress observed during protracted ethanol abstinence. *Alcohol* 29: 55–60.
- Vale W, Spiess J, Rivier C, Rivier J (1981) Characterization of a 41-residue ovine hypothalamic peptide that stimulates the secretion of corticotropin and  $\beta$ -endorphin. *Science* 213: 1394–7.
- Vendruscolo LF, Estey D, Goodell V, Macshane LG, Logrip ML, Schlosburg JE, McGinn MA, Zamora-Martinez ER, Belanoff JK, Hunt HJ, Sanna PP, George O, Koob GF, Edwards S, Mason BJ (2015) Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. *J Clin Invest* 125: 3193–7.
- Vendruscolo JCM, Tunstall BJ, Carmack SA, Schmeichel BE, Lowery-Gionta E, Cole M, George O, Vandewater S, Taffe M, Koob GF, Vendruscolo LF (2018) Compulsive-like sufentanil vapor self-administration in the rat. *Neuropsychopharmacology* 43: 801–9.
- Volkow ND, Gordon JA, Koob GF (2021) Choosing appropriate language to reduce the stigma around mental illness and substance use disorders. *Neuropsychopharmacology*, in press.
- Volkow ND, Koob GF (2015) Brain disease model of addiction: why is it so controversial? *Lancet Psychiatry* 2: 677–9.

- Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, Perez-Stable E, Riley WT, Bloch MH, Conway K, Deeds BG, Dowling GJ, Grant S, Howlett KD, Matochik JA, Morgan GD, Murray MM, Noronha A, Spong Y, Wargo EM, Warren KR, Weiss SRB (2018) The conception of the ABCD Study: from substance use to a broad NIH collaboration. *Dev Cogn Neurosci* 32: 4–7.
- Voon V, Grodin E, Mandali A, Morris L, Weidacker K, Kwako L, Goldman D, Koob GF, Momenan R (2020) Addictions NeuroImaging Assessment (ANIA): towards an integrative framework for alcohol use disorder. *Neurosci Biobehav Rev* 113: 492–506.
- Walter R, Van Ree JM, De Wied D (1978) Modification of conditioned behavior of rats by neurohypophyseal hormones and analogues. *Proc Natl Acad Sci USA* 75: 2493–2496.
- Weiss F, Ciccocioppo R, Parsons LH, Katner S, Liu X, Zorrilla EP, Valdez GR, Ben-Shahar O, Angeletti S, Richter RR (2001) Compulsive drug-seeking behavior and relapse: neuroadaptation, stress, and conditioning factors. In: Quinones-Jenab V (ed) *The Biological Basis of Cocaine Addiction* (series title: *Annals of the New York Academy of Sciences*, vol. 937). New York Academy of Sciences, New York, pp. 1–26.
- Wise RA, Koob GF (2014) The development and maintenance of drug addiction. *Neuropsychopharmacology* 39: 254–62.