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Research Advances Understanding of Opioid Addiction in Face of Public Health Crisis

Drugs influence brain development, fear and anxiety, memory

WASHINGTON, DC — As the United States grapples with the devastating effects of an opioid epidemic, researchers are making progress in advancing our understanding of opioid addiction–related health issues, according to studies presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Approximately 90 Americans die every day from opioid overdoses, according to the National Institute on Drug Abuse, creating what public agencies have referred to as both an epidemic and a crisis. Opioids, which include prescription pain medications such as morphine and oxycodone as well as illegal substances such as heroin and fentanyl derivatives, alleviate pain and can induce euphoria by interacting with receptors on nerve cells in the nervous system. They also have high abuse potential, meaning that clinical uses of opioids bear added risks associated with substance use-disorders, physical dependence, and withdrawal.

Today's new findings show that:

- A common genetic variation in an opioid receptor gene protects against behavioral effects of prenatal opioid exposure in mice (Shivon April Robinson, abstract 702.15, see attached summary).
- Opioid addiction heightens fear and anxiety responses to traumatic events in mice, potentially explaining the prevalence of post-traumatic stress disorder in individuals dependent upon opioids (Zachary T. Pennington, abstract 247.08, see attached summary).
- "Erasing" drug memories using a novel procedure reduces heroin cravings and relapses when administered within one hour of methadone treatment (Ping Wu, abstract 515.03, see attached summary).
- Critically ill, full-term infants exposed to opioids through repeated anesthesia and prolonged sedation show signs of abnormal brain development within the first year of life (Dusica Bajic, abstract 284.04, see attached summary).

Other recent findings discussed show that:

- A diet rich in high fructose corn syrup reduces neural and behavioral responses to oxycodone in rats, potentially encouraging overuse of the drug and increasing risk of dependence (Meenu Minhas, abstract 418.16, see attached summary).

"Given the current public health crisis as well as the medical importance of safe, effective pain medication, we need to learn as much as possible about the effects and interactions of opioids with the brain and nervous system," said press conference moderator Edward Bilsky, PhD, provost and professor of biomedical sciences at Pacific Northwest University of Health Sciences. "These new findings hold promise for advancing treatment options for substance-use disorders and also informing clinical uses of these drugs as analgesics in the treatment of acute and chronic pain."

This research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about opioid addiction on *BrainFacts.org*.

Related Neuroscience 2017 Presentation
Symposium: Circuit and Synaptic Plasticity Mechanisms of Drug Relapse
Tuesday, Nov. 14, 1:30–4 p.m., WCC Ballroom B

Abstract 702.15 Summary

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A Variation in Opioid Receptor Gene May Influence Effects of Prenatal Drug Exposure

Genetic variant mitigated morphine-induced deficits in social attachment, emotional regulation in mice

A common gene variant may mitigate some of the negative developmental effects of prenatal exposure to opioid drugs like heroin and oxycodone, according to animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Opioid abuse and addiction among pregnant women in the United States increased nearly fivefold from 2000 to 2012. Opioid exposure while in the womb puts infants at high risk for neonatal abstinence syndrome (NAS), a complex set of physical withdrawal symptoms that can include fussiness, sleeplessness, gastrointestinal distress and, in some cases, seizures. Despite NAS's being one of the leading causes of neonatal hospital admissions in the U.S., the biological factors that affect the syndrome's severity are unknown. Moreover, the longer-term developmental effects and the impacts of neonatal opioid exposure and withdrawal on mental health later in life are not well documented.

About 25 percent of people carry a DNA variation in *Oprm1*, an opioid receptor gene, and this variant has been associated with shorter NAS-related hospital stays. Using a mouse model, researchers investigated whether this variant affects the developmental and behavioral consequences of morphine exposure during a time equivalent to the third trimester of human pregnancy.

They found that, regardless of the presence of the genetic variation, all of the morphine-exposed baby mice, called pups, took longer than non-exposed pups to reach developmental milestones such as eye-opening and grasping. However, the *Oprm1* variant did seem to protect against later behavioral effects of morphine exposure. For example, in male pups without the genetic variant, morphine exposure significantly reduced vocalization during social isolation, indicating deficits in social attachment. In addition, when tested in adolescence, morphine-exposed female mice without the variant exhibited reduced reactivity to a novel environment, which may reflect disturbances in emotional processing. These negative effects were absent in morphine-exposed pups with the variant.

"Our results demonstrate that the *Oprm1* variation appears to play an important role in behavior associated with social attachment and emotional regulation following prenatal morphine exposure," said lead author Shivon Robinson, PhD, a postdoctoral fellow in pharmacology professor Julie Blendy's lab at the University of Pennsylvania. Next the researchers plan to explore the effects of opioid exposure throughout gestation to further investigate nervous system mechanisms that underlie NAS.

Research was supported with funds from the National Institute on Drug Abuse and the National Institute of General Medical Sciences.

Scientific Presentation: Wednesday, Nov. 15, 10–11 a.m., WCC Halls A–C

11279. Neurobehavioral effects of early opioid exposure in mice: Influence of the Oprm1 A112G single nucleotide polymorphism
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TECHNICAL ABSTRACT: Infants exposed to opioids in utero are at high risk of developing Neonatal Abstinence Syndrome (NAS), a combination of somatic withdrawal symptoms including high pitched crying, irritability, gastrointestinal distress, and in some cases seizures. Despite being one of the leading causes of neonatal hospital admissions in the U.S., the factors impacting NAS severity are unknown. Furthermore, how this experience impacts behavior later in life has not been well documented. A potential genetic influence of NAS outcome may be a single nucleotide polymorphism (SNP) in the opioid receptor gene (OPRM1), which has recently been shown to be associated with shorter length of stay in the hospital for infants with this SNP (Wachman et al., 2015). Using our mouse line possessing the equivalent nucleotide/amino acid substitution in the OPRM1 gene (A112G), we sought to determine if this SNP modulates the short and/or long term behavioral effects of neonatal opioid exposure in mice. Newborn pups harboring either the A/A or G/G alleles were injected with morphine (10mg/kg) from postnatal day (PND) 1-14 (equivalent to the third trimester of human gestation) and observed for emergence of developmental milestones and withdrawal symptoms. We observed delays in reaching important developmental milestones, such as eye opening, forelimb grasping and ambulations in an open field, with morphine-exposed mice taking longer to reach criteria and trends toward a genotype x morphine interaction. To determine if neonatal morphine exposure and withdrawal produces long lasting effects on behavior, mice exposed to morphine from PND 1-14 were assessed on anxiety-like behavior and drug sensitivity in adulthood. Morphine treated animals showed increased anxiety-like behavior, as measured by reduced time spent in the open arms of the elevated zero maze. Sensitivity to repeated morphine administration assayed through locomotor response showed that morphine-exposed animals exhibit significantly blunted locomotor sensitization to repeated morphine. The further development of a mouse model of NAS will allow for more in depth investigation into the influence of genetic variability as well as provide insights into the underlying neurobiology of this syndrome.

Abstract 247.08 Summary

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Opioid Use Before or After Trauma May Worsen Post-Traumatic Stress Disorder Symptoms

Findings in mice suggest anxiety sufferers who 'self-medicate' with opioids may aggravate symptoms

Chronic drug exposure enhances fear and stress responses in the brains of mice, a finding that may help explain why opioid users are more likely than non-users to suffer post-traumatic stress disorder. This new preclinical research was released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Fear and anxiety disorders frequently occur together with substance abuse. Sufferers of post-traumatic stress disorder (PTSD), a condition characterized by fear and anxiety responses that persist following a traumatic event, are often thought to abuse drugs in an effort to reduce their symptoms — behavior often referred to as "self-medication." But little research has examined the inverse: the potential of chronic drug use to provoke fear and anxiety.

To investigate whether addiction may predispose individuals to PTSD, researchers measured fear responses in morphine-treated mice, both immediately after traumatic stress and later in a new environment. When subjected to trauma (a series of shocks), mice that had prior morphine exposure showed heightened signs of fear compared to unexposed mice. In a later test in a different physical environment, the morphine-exposed mice displayed a hypersensitive reaction to mild adverse stimulation, a response consistent with human PTSD. In another experiment, morphine given to mice after a traumatic event also increased their fear responses. In all cases, the heightened fear responses were temporary, lasting from a week to a month after drug use ended.

"These results suggest that prior opioid exposure activates the stress systems that respond to trauma, enhancing fear and anxiety," said Zachary T. Pennington, a PhD candidate at the University of California, Los Angeles. "Our data also suggest that self-medicating with opiates after trauma could possibly worsen fear and anxiety symptoms rather than alleviate them."

Future research will seek to verify whether the morphine doses administered to the animals are relevant to drug use among humans and will investigate the biological processes underlying these changes in fear learning.

Research was supported with funds from the National Institute of Mental Health.

Scientific Presentation: Sunday, Nov. 12, 4–5 p.m., WCC Halls A–C

6465. Chronic opiate administration produces a long-term potentiation of fear and anxiety in a model of post-traumatic stress disorder
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TECHNICAL ABSTRACT: Fear and anxiety disorders are highly comorbid with substance use disorders. Although traditional views on this relationship have proposed that substance use ensues in an effort to reduce fear and anxiety (i.e. self-medication), little research has examined the influence chronic drug use has on fear and anxiety. We assessed the impact of a chronic escalating regimen of morphine and withdrawal on fear in a mouse model of post-traumatic stress disorder: stress-enhanced fear learning (SEFL). Mice that received morphine exposure and withdrawal 1 week prior to a 10-shock trauma session displayed heightened freezing during the trauma session, without displaying differences in shock reactivity. When subsequently given a mild aversive stimulus, morphine treated animals showed a robust sensitization of the enhanced fear learning that is typically seen in traumatized animals. However, fear was not elevated in animals given morphine that had not experienced trauma. These results suggest that the potentiation of stress systems by trauma is exacerbated by prior opiate exposure. In a separate experiment, we showed that when morphine is given after the traumatic stressor, it also has the ability to augment fear responses, indicating that opiate exposure isn't merely augmenting trauma sensitivity. Lastly, morphine treated animals expressed increased anxiety in an elevated plus maze (a test that does not involve a painful stimulus), and did not show altered reactivity to a range of shock amplitudes, negating the possibility that the previous effects on fear behaviors were the consequence of heightened pain sensitivity. To our knowledge, this is the first demonstration in which chronic drug exposure is able to produce a lasting enhancement of fear systems, and may be of relevance to the comorbidity between fear and substance use disorders.

Abstract 515.03 Summary

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"Erasing" Drug Memories Improves Effectiveness of Methadone-Based Heroin Treatment

Novel approach may reduce heroin cravings and relapses

A novel procedure to "erase" drug memories reduces drug cravings and relapses in individuals addicted to heroin and undergoing methadone maintenance treatment, according to research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

A major problem in the treatment of substance use disorders is how to prevent drug cravings, even after long-term abstinence. When people who have experienced habitual patterns of drug use are exposed to internal or external drug-related cues (e.g., people, places, or items associated with prior abuse) or stressors, it triggers memories of the high of previous drug use and can lead to intense cravings.

Previous animal studies by this research group demonstrated the effectiveness of a novel procedure they developed that erases these drug memories. The approach, called memory retrieval-extinction, is based on the idea that reactivation of memories can open them up to modification or even elimination. Researchers administered a small dose of a drug (cocaine or heroin) to rats to reactivate the memory of drug taking but not trigger the high and then showed the rats drug-associated cues, such as tone and light. Researchers found that these sessions broke the connection between the cues and desire for the drug in the rats, preventing relapses. However, the addictive properties of heroin make using even small amounts of the drug controversial for use in human subjects.

In their new study, the researchers adapted their memory-erasure procedure for people recovering from heroin use. They tested methadone, a drug commonly used to wean people off of heroin, as a trigger to reactivate memories of drug use. When used within an hour of methadone treatment, the retrieval-extinction procedure successfully inhibited drug cravings and relapse in this population. While the one-hour time frame for treatment sessions was the most effective, sessions given six hours after methadone administration also reduced heroin cravings at early points during the follow-up period.

"These findings demonstrate that using methadone as part of a memory-treatment strategy may be a promising method for decreasing long-term drug cravings and relapses in people recovering from heroin and other substance-use disorders," said lead author Ping Wu, MD, of Peking University.

Research was supported with funds from the National Key Basic Research, the National Key Research and Development Program of China, and the National Natural Science Foundation of China.

Scientific Presentation: Tuesday, Nov. 14, 10–11 a.m., WCC Halls A–C

12126. Methadone induced retrieval extinction procedure inhibits the drug craving and relapse in heroin addicts under methadone maintenance treatment

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TECHNICAL ABSTRACT: Conditioning between drug-associated environment cues (conditioned stimulus, CS) and drug effects (unconditioned stimulus, UCS) plays a major role in drug addiction, and responses to drug-associated cues persist during prolonged abstinence. We previously reported that CS memory retrieval-extinction procedure decreases relapse of cocaine and heroin seeking in rats and heroin craving in humans. However, the CS retrieval-extinction procedure could only erase drug memory associated with the reactivated CS, and it was not effective after prolonged abstinence. In contrast, the inhibitory effect of UCS retrieval-extinction manipulation on drug seeking in rats was also observed in the presence of cues that were not reactivated or after long-term abstinence. Using methadone as the UCS, the present study investigated the effect of UCS retrieval-extinction on cue induced drug craving and relapse in heroin addicts. Eighty-nine male heroin addicts under methadone maintenance treatment were randomly divided into 3 groups: 1) Methadone, 2) Methadone+10-min delay+ extinction, 3) Methadone+6-h delay+ extinction. The subjects in Group 1 took methadone as usual, while the subjects in Group 2 and 3 underwent extinction sessions 10 min or 6 h after methadone intake 3 times per week for 4 weeks. All the subjects were followed up for 6 m to test the changes of heroin craving, relapse, and dose of daily methadone use. We also conducted morphine urine tests each week during the 4 weeks' intervention and each month during the follow up. Seventy-eight heroin addicts completed the intervention and were included for statistical analysis. There was no significant difference in cue induced heroin craving, dose of daily methadone intake, depression, anxiety, as well as demographic characteristics at baseline among the three groups. After 4 weeks' methadone-induced retrieval extinction manipulation, both the subjects in Group 2 and Group 3 showed significantly decreased heroin craving compared with Group 1. The inhibitory effect on heroin craving persisted for 4 m in Group 2, but only persisted for 2 m in Group 3. Both the accumulative drop-out rates and relapse rates of Group 2 were significantly lower than Group 1 and Group 3. These findings demonstrated that the methadone induced retrieval extinction strategy could be a promising method for decreasing drug craving and relapse in heroin addicts.

Abstract 284.04 Summary

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Prolonged Sedation in Critically-Ill, Full-Term Infants May Lead to Brain Abnormalities

Higher sedative doses correlate with more brain MRI anomalies during first year of life

Full-term infants who undergo repeated anesthesia and prolonged sedation are at risk for changes in brain development, according to a study released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Developmental impacts of prenatal exposure to sedatives have been widely studied, but less is known about the immediate and long-term neurological and developmental effects of prolonged sedation when administered to critically ill infants after birth. Prolonged administration of opioids and benzodiazepines — two classes of drugs commonly used for pain and sedation management in infants undergoing surgery and other procedures — is associated with a high incidence of drug tolerance and dependence. Although some negative long-term outcomes have been associated with such drug exposures in infants, these studies could not exclude other possible causes such as prematurity or heart problems.

To study neurological effects of prolonged sedation, researchers conducted MRI scans on full-term infants who underwent life-saving surgery that required prolonged exposure to the common sedatives morphine and midazolam before one year of age. Brain imaging showed several brain MRI anomalies that were not present in healthy infants, including abnormalities in gray and white matter structures and the ventricles (the fluid-filled cavities within the brain). The number of brain MRI abnormalities significantly correlated with the average daily dose of these sedative drugs: The higher the daily dose, the more MRI irregularities were seen. The patients also had more brain fluid and a smaller total brain volume compared to healthy infants — a pattern that has been previously associated with long-term neurodevelopmental outcomes such as autism spectrum disorder. Taken together, these preliminary findings indicate a potential negative impact of prolonged sedation on brain growth during the first year of life, researchers said.

"We were surprised to find higher incidence of brain abnormalities in full-term infants who underwent life-saving surgery that required prolonged sedation," said senior author Dusica Bajic, MD, PhD, of Boston Children's Hospital. "The constellation of MRI irregularities suggests prolonged sedation may potentially contribute to delayed brain growth."

Future investigations aim to explore the neural mechanisms of the observed developmental effects and whether early sedation exposure may lead to long-term neurobehavioral impacts.

Research was supported with funds from the National Institutes of Health and Boston Children's Hospital.

Scientific Presentation: Monday, Nov. 13, 8 a.m.–noon, WCC Halls A–C

13792. Correlation study of prolonged sedation and incidental MRI findings in full-term infants
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TECHNICAL ABSTRACT: Prolonged administration of opioids and benzodiazepines used for pain and sedation management in the youngest of patients is associated with a high incidence of drug tolerance and dependence. The clinical impact of such treatment on the full-term infants is largely unknown. We hypothesized that prolonged sedation with opioids and benzodiazepines in full-term infants younger than 1 year is associated with (1) increased incidence of brain abnormalities as per brain MRI scan, (2) increased CSF volumes, and (3) decreased brain volumes in comparison to healthy controls. Subjects were compared between two groups as per IRB approval at the Boston Children's Hospital. Subjects underwent research scan at 3T MRI scanner for 3D T-1 and T2-weighted anatomical images, while charts were reviewed for quantification of sedation. End-point analyzes included: (1) length of sedation and weaning (days), (2) total treatment doses per patient (mg/kg/day), (3) average daily doses during sedation and weaning (mg/kg/day ± SD), (4) number of anesthesia events, (5) number of incidental findings on brain MRI reports, and (6) estimated normalized cerebrospinal and brain volumes using MANTiS segmentation. Pearson's correlation coefficient was used to measure the linear relations between the different variables analyzed. Morphine and midazolam were the two drugs used the most frequently for prolonged sedation and were administered at the highest doses. We report significant positive linear relationships for the average daily dose of received morphine and midazolam with the number of neuroradiological findings (e.g. abnormalities in extra-axial space, ventricular system, parenchyma, and/or white matter structures) that were not present in any of the controls. There was no significant relationship between the average daily dose of morphine or midazolam despite the apparent positive trend with cerebrospinal fluid volume, and negative trend with estimated brain volume. Given the current standard of care using these drugs for prolonged sedation, future investigations of gray and white matter organization in at-risk full-term infants can provide crucial information of how prolonged sedation can affect brain development and potentially lead to long-term neurobehavioral sequelae.

Abstract 418.16 Summary

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High Fructose Corn Syrup Dulls Rewarding Effects of Opioids in Rats

Dampened responses to oxycodone could encourage consumption of larger amounts of the drug

A diet rich in sugars may reduce the pleasurable effects of oxycodone, according to recently published preclinical research presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Refined sugar has been shown to promote compulsive food intake by activating the brain's rewards centers in much the same way as drugs with high abuse potential. Opioid abuse is associated with poor dietary habits, including a preference for sugar-rich foods over fat- or protein-rich diets as well as malnutrition due to eating too little or choosing nutrient-poor food. These connections have led to questions about whether sugar consumption may affect opioid dependence.

To explore how a sugar-rich diet interacts with opioid use, researchers investigated whether unlimited access to high fructose corn syrup (HFCS) altered rats' neural and behavioral responses to oxycodone, a widely abused prescription opioid. At the neural level, HFCS exposure decreased the drug-induced release of dopamine, a desire-promoting neurotransmitter active in the brain's reward circuits. HFCS exposure also reduced drug-induced locomotor behavior. These findings suggest that a high-sugar diet may dampen the reward associated with a given dose of oxycodone and consequently promote intake of higher levels of the drug.

"Our experiments show that chronic pre-exposure to high-fructose corn syrup impacted both the neural and behavioral responses to oxycodone, resulting in changes likely to impact drug-taking and drug-seeking behavior," said co-lead author Meenu Minhas, a PhD student at the University of Guelph in Ontario, Canada. "Taken together, these results suggest that nutrition, and sugar intake in particular, can influence some responses to opioids, a finding that may be relevant both to clinical uses of opioids and to treating addiction."

Research was supported with funds from the Natural Science and Engineering Research Council of Canada.

Scientific Presentation: Monday, Nov. 13, 4–5 p.m., WCC Halls A–C

8784. Can high fructose corn syrup alter behavioral and neural responses to oxycodone?
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TECHNICAL ABSTRACT: The food addiction hypothesis suggests that refined sugars such as high fructose corn syrup (HFCS) can promote addictive-like behaviors. This leads to the prediction that sugars and drugs of abuse interact at both neural and behavioral levels. The present study examined whether rats chronically pre-exposed to high fructose corn syrup (HFCS; 55% fructose to 45% glucose) altered responses to oxycodone (OXY), a widely abused prescription opioid. Since sugars can activate opioid receptors in the ventral tegmental area to enhance dopamine (DA) release in the nucleus accumbens (NAc) to affect reward processes, we investigated whether chronic HFCS pre-exposure affected responses to: OXY- place preference, OXY-induced locomotor sensitization, and OXY-induced elevation in DA concentrations in the NAc. Male Sprague-Dawley rats received in their home cages: 0% HFCS 24h a day (n = 70); 50% HFCS 24h a day (continuous access group, CONT; n = 84); or 50% HFCS 12h a day (intermittent access beginning 4 h into the dark cycle, INT; n = 28) for 26 days. INT sugar access was employed as it leads to "bingeing" behavior, which is linked to the neural alterations that cause enhancements in reward and motor responses to stimuli. Following a 9-day sugar free period, animals were tested on one of the following: (1) place conditioning (biased design) involving: pre-test, place conditioning (0, 0.16, or 2.5 mg/kg OXY SC; 3 pairings each over 6 days), and a test of preference; (2) locomotor sensitization involving context-dependent treatment with OXY (0, 0.16, or 2.5 mg/kg SC) over 5 days, followed by a 9-day drug-free period, following which locomotor activity was measured in the drug-paired context, both in the absence and 24 hrs later in the presence of OXY; (3) in vivo microdialysis of extracellular DA in the NAc during a 1hr baseline and 3 hrs following an injection of OXY (0 or 2.5 mg/kg SC). It was found that 0.16 and 2.5 mg/kg OXY produced a place preference, but this was not modified by HFCS pre-treatment. Furthermore, HFCS pre-treatment decreased OXY-induced, but not context-induced locomotion. Microdialysis data revealed that HFCS pre-treatment decreased the OXY-induced dopaminergic response in the NAc. Taken together, the current experiments indicate that chronic HFCS pre-exposure blunted the psychomotor and dopaminergic response to OXY, but did not alter OXY conditioned locomotion or reward. These results suggest that opioids and sugars interact at both behavioral and neural levels, indicating that nutrition has the potential to influence some responses to opioids, and this may be relevant to the licit and illicit use of these drugs.