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The neuroscience of pain, addiction, and anesthesia

Researchers and clinicians have long been interested in the mechanisms of pain, anesthesia, and addiction. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (Raja et al., 2020). Drug addiction refers to a condition of reliance that develops from regular drug consumption, which may lead to withdrawal symptoms when use is halted. Anesthesia involves the complete loss of consciousness induced by an inhaled or intravenous anesthetic (Tosello et al., 2022). In this special collection, *Zoological Research* presents research findings focused on pain, addiction, and anesthesia.

The parabrachial nucleus (PBN), a gray matter structure located near the cerebellum at the pons, regulates various physiological activities, such as breathing, sleeping, and feeding, and plays a crucial role in pain transmission within the central nervous system (Chiang et al., 2019). In this issue, Ke et al. (2024) provide a comprehensive analysis of the distinct functional roles of lateral PBN (lPBN) subnuclei in mediating sustained pain. Through neuroanatomical tracing, cell-specific ablation, and chemogenetic silencing, they report that neurons expressing the substance P receptor (NK1R) in the central/superior subdivision of the lPBN (slPBN) are crucial for mediating pain-associated self-care behaviors and aversive memory. These neurons can be activated by sustained noxious thermal and mechanical stimuli applied to the skin or deep tissues, such as muscle or bone. In contrast, the external subdivision of the lPBN (elPBN) is implicated in defensive reactions to external threats but not in sustained pain responses. This research contributes to our understanding of how different brain regions coordinate responses to noxious stimuli and highlights the complexity of pain processing in the central nervous system.

Mild traumatic brain injury (mTBI), accounting for 80%–90% of all TBI cases, is associated with post-traumatic headache (PTH), a common secondary headache condition (Jiang et al., 2019; Lucas et al., 2014). In this issue, Yang et al. (2024) investigate the effects of mTBI on PTH, exploring structural and functional brain abnormalities, particularly metabolic changes in the cerebellum, temporal cortex, and hippocampus. Metabolic analyses reveal significant alterations in GABA and glutamate levels, suggesting their potential as biomarkers for PTH. These findings imply that the cerebellum and temporal cortex may be key regions in regulating PTH, providing targets for future non-invasive clinical treatments.

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The mechanisms underlying drug addiction are complex and involve multiple cell types within the brain. Microglia, as essential immune cells of the central nervous system, play an important role in the progression of drug addiction. In this issue, Lin & Wang (2023) provide valuable insights into the role of microglia in drug addiction. Drug abuse can activate microglia in the brain, which subsequently trigger cytokine production, leading to tissue damage and neuroinflammation. The authors suggest that targeting microglia and their activation may offer a potential therapeutic approach to alleviate drug addiction and related neuroinflammatory diseases. They also summarize specific strategies, including the inhibition of TLR4 signaling associated with substance abuse-induced microglial activation and pharmacological depletion of microglia. Given the diverse functional traits of microglia in response to repeated stimulation, exploring and targeting specific microglial subsets provides a promising novel strategy for the treatment of drug addiction.

Immunotherapies such as vaccines, monoclonal antibodies, and catalytic enzymes have gained traction as potential options for the prevention and treatment of substance use disorders (SUDs). In this issue, Wang et al. (2024) discuss recent advances in the development of SUD vaccines. These vaccines stimulate an immune response to the substance of abuse, producing antibodies that prevent the substance from crossing the blood-brain barrier, thereby blocking its rewarding effects. Developing effective vaccines is challenging due to the need to elicit an immune response to small molecules, or haptens, which are not typically recognized by the immune system. To address this, haptens can be conjugated with larger carrier proteins to form a complex that can be recognized by the immune system. Here, the authors propose a novel biomimetic strategy using polymer carriers instead of traditional protein carriers, offering advantages such as tunable properties and reduced risk of biological contamination. This approach also incorporates molecular adjuvants to enhance vaccine efficacy. The development of these next-generation vaccines aims to provide long-term protection against substance use with minimal doses, although concerns about potential risks, such as increased drug intake to counteract the vaccine's effects, need to be addressed.

General anesthesia is widely used in clinical practice, yet the mechanism by which it causes loss of consciousness remains poorly understood. In this issue, Qiu et al. (2023) employ *in vivo* fiber photometry and genetically encoded neurotransmitter sensors to investigate the dynamics of five key neurotransmitters (γ-aminobutyric acid (GABA), glutamic acid, norepinephrine, acetylcholine, and dopamine) in the medial prefrontal cortex and primary visual cortex of mice under propofol and sevoflurane anesthesia. They reveal a synchronized increase in GABA, glutamate, norepinephrine, and acetylcholine concentrations during propofol anesthetic-induced loss of consciousness (aLOC), with dopamine levels

increasing only at surgical doses of propofol. In contrast, the concentrations of these neurotransmitters show a general decrease during sevoflurane-induced aLOC. These results imply that the synchronization of neurotransmitter interaction networks may play a crucial role in the loss of consciousness induced by anesthesia.

General anesthesia is closely linked to developmental abnormalities of the central nervous system. In this issue, Liang et al. (2023) investigate the neurodevelopmental effects of sevoflurane, a commonly used anesthetic, on neonatal mice and assess the potential therapeutic benefits of davunetide. Their study reveals that neonatal exposure to sevoflurane leads to long-term social and cognitive impairments in mice, associated with decreased expression of the ADNP protein. Previous research has demonstrated that recurrent sevoflurane administration in the early postnatal period can result in persistent suppression of Wnt/β-catenin signaling in hippocampal neurons and oligodendrocytes (Liang et al., 2021), while ADNP-derived davunetide can mitigate these impairments by restoring synaptic function and up-regulating Wnt/β-catenin signaling. These findings suggest that ADNP plays a critical role in the neurodevelopmental toxicity of anesthetics, with davunetide showing promise as a treatment for the prevention of long-term damage from anesthetic exposure.

General anesthetics can influence brain function by interacting with neurons and impacting glial cells, particularly oligodendrocytes. In this issue, Hang et al. (2024) provide a comprehensive review of the neurotoxic effects of general anesthetic agents (GAAs) on oligodendrocytes in the developing brain. Oligodendrocytes are crucial for myelin sheath formation, a critical process for nerve impulse transmission. The authors discuss how GAAs can disrupt oligodendrocyte proliferation, differentiation, and apoptosis, potentially leading to long-term cognitive impairments. Their review further highlights the impact of GAAs on various signaling pathways and metabolic processes, which can alter gene expression and impair myelin sheath construction. The authors also emphasize the need for additional research to elucidate the precise mechanisms by which anesthetics target oligodendrocytes and to develop strategies to reduce the incidence of adverse reactions associated with general anesthetic agents.

Current research on pain, drug addiction, and general anesthetics has made significant progress, yet several limitations and challenges remain. The transition from acute to chronic pain is not well characterized, and the underlying mechanisms are still being explored. Future efforts should focus on the development of personalized pain management strategies based on individual genetic and neurobiological characteristics. The neurobiological basis of addiction is complex and not fully understood, involving multiple brain systems and neurotransmitters. In addition, the potential neurotoxic effects of anesthetics on developing brains are not fully understood. By integrating multidisciplinary research from fields such as neuroscience, psychology, pharmacology, and social science, it is anticipated that our understanding of pain, addiction, and anesthesia will deepen, leading to the development of more effective treatments and interventions.

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