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Special Issue – Neurochemistry of Reward-Seeking

Title:

Should we or shouldn't we?

Sub-title:

Preface to the Special Issue "Neurochemistry of Reward-Seeking"

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Abstract

Reward-seeking is critical for survival. Learning about the relationship between actions and outcomes helps us to make decisions and select behaviours that result in a specific outcome. This special issue entitled “The Neurochemistry of Reward-Seeking” addresses this crucial facet of behaviour and brings together a number of key thought-leaders to provide a timely update on the circuitry, chemistry and mechanisms underlying different aspects of reward-seeking. The reviews in this issue canvass unanswered questions in the field and provide a degree of forethought about how we may advance our understanding of reward-seeking by embracing novel technology alongside existing scholarship. This issue also highlights the neurochemical complexity of reward-seeking, and the reader will uncover both distinct and shared circuits and transmitters driving various forms of reward-seeking. Accordingly, we hope that this special issue will provide a valuable resource for the field and trigger future research on this topic.

Key words: reward, addiction, behaviour, neurochemistry, circuits, receptors

[Main text, no separate header]

Reward-seeking is a complex and necessary function, with multiple drivers. This concept is elegantly captured in the words of Ayn Rand (1905-1982): “You seek escape from pain. We seek the achievement of happiness. You exist for the sake of avoiding punishment. We exist for the sake of earning rewards”. The aim of this special issue is to delve into the multiple factors that shape and guide this behaviour.

Social interactions and their consequences are a major factor that shape emotional development. Manduca and colleagues discuss this issue highlighting how animal models can be used to interrogate key forms of social interaction, such as mother-infant bonding and peer-group interactions. They describe paradigms that enable various components of these social interactions to be assessed and discuss the role of key transmitters in these behaviours, including opioids, endocannabinoids, dopamine and oxytocin systems (Manduca et al., 2021). Sensory-specific learning more broadly guides how we choose actions that will result in a desired outcome. Laurent and Balleine (2021) discuss a circuit and neurochemical mechanism implicated in a form of cellular memory that assists action selection, which forms the basis of how one chooses based on the knowledge of likely future consequences. This theme is extended by Nall and co-authors who propose circuitry that is necessary for drug but not natural reward-seeking (Nall et al., 2021). Despite the distinct neural correlates of natural and drug rewards, certain biological substrates are implicated in both these forms of reward-seeking. One such example is the neuropeptide orexin, which is expressed within neurons of the lateral hypothalamus (Mahler et al., 2012). In this issue, the orexin system is discussed in terms of homeostatic versus hedonic feeding and the motivation for highly salient rewards (Muthmainah et al., 2021). Another system seemingly able to modulate both natural and drug rewards is the gut-brain-axis, implicating the microbiome as a potential intervention target in the future treatment of dysfunctional reward-seeking (Garcia-Cabrerizo et al., 2021).

The transition from “normal” to “aberrant” reward-seeking has been associated with the development of compulsive behaviour. Likewise, impulsive actions are typically pursued in the absence of forward-thinking about consequences. Pre-existing versus drug-induced impulsivity and the relationship of poor impulse control to compulsion are discussed within the context of whether overlaps in the neurochemistry of impulsivity and compulsivity represent risk factors for the transition to addiction-like behaviour in animal models (Jones et al., 2021). Drug use comes with consequences, the valence of which can shape future choices (as flagged above, see Laurent and Balleine, 2021). This issue is reviewed by Piantadosi and colleagues who discuss how an aversive experience resulting from specific reward-seeking is integrated into subsequent actions. Further, they describe the neurochemistry that underpins punishment learning and risky decisions, with a particular emphasis on dopamine (Piantadosi et al., 2021). Dopamine is also the primary focus of Liu and McNally’s review on relapse. The authors provide an elegant demonstration of the pivotal yet complex role of dopamine in relapse to drug/alcohol-seeking (Liu and McNally, 2021). For example, different forms of relapse are driven by divergent circuits involving discrete groups of dopamine neurons with distinct patterns of cellular activation. Their review underscores the need to probe the neural substrates underpinning reward-seeking with high resolution if we are to fully understand how specific brain pathways drive these behaviours.

In this issue, three reviews address different, yet complementary issues pertinent to alcohol use and abuse. Domi and colleagues describe animal models for compulsive alcohol-seeking and relapse, and discuss neurotransmitter systems implicated in these behaviours (Domi et al., 2021). On the heels of this review, the central amygdala is discussed as a key node for interactions between stress and alcohol, and potential sex differences in these interactions (Walker, 2021). A major research question moving forwards is to elucidate the specific role(s) of neurochemically diverse and heterogeneous cell groups within the central amygdala in relation to stress, anxiety and alcohol use/abuse. The third alcohol-related article provides a summary of how the insular cortex responds to both alcohol and alcohol-related cues both during active drinking and

abstinence, alongside the involvement of the insular cortex in driving alcohol-seeking in high risk situations (Campbell and Lawrence, 2021).

Nicotine is another legal drug of abuse, and repeated use of nicotine mediates adaptations in both reward and aversion circuits that ultimately shapes future tobacco (nicotine) use patterns (Wills and Kenny, 2021). Another widely smoked drug is cannabis (although it is also taken via other routes). In this regard, Kesner and Lovinger (2021) provide a comprehensive review on the behavioural effects of cannabis and the cellular and molecular mechanisms associated with cannabis use, tolerance, dependence and withdrawal. They conclude by calling for governments to consider rescheduling the regulatory control of cannabis and phytocannabinoids so they are available for preclinical and clinical studies to proceed in parallel in order to enable deeper understanding of the effects of cannabis and facilitate medication development.

Mantsch and colleagues review the relationship between stress and cocaine-seeking, with a focus on noradrenaline and corticotropin releasing factor (CRF) and how glucocorticoids interact with multiple neurochemical systems in specific brain nuclei to promote relapse in the face of stress (Caccamise et al., 2021). The final article in this issue by Schenk and Highgate (2021) provides a timely update on the interaction of MDMA with dopamine and serotonin systems, and the role of Trace Amine Associated Receptor 1 (TAAR1) in the maintenance of MDMA self-administration (Schenk and Highgate, 2021).

While by no means exhaustive, this special issue ties together several distinct yet complementary viewpoints on various components of natural versus drug reward, including: the consequences of long-term drug use, relapse, decision-making in the face of adversity or risks, and stress and drug interactions for alcohol and cocaine. The goal of this issue is to update the field, provide a vision for future research and highlight how current and emerging technologies can facilitate the interrogation of increasingly complex questions about how the brain drives behaviour. We hope you enjoy reading these articles.

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Conflict of interest statement

Andrew J. Lawrence is the Editor-in-Chief of the Journal of Neurochemistry.

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