Trends in Cognitive Sciences

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REVIEWS

Review

Can't or Won't? Immunometabolic Constraints on Dopaminergic Drive

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Inflammatory cytokines have been shown to have a direct effect on mesolimbic dopamine (DA) that is associated with a reduced willingness to expend effort for reward. To date, however, the broader implications of this communication between inflammation and mesolimbic DA have yet to be explored. Here, we suggest that the metabolic demands of chronic low-grade inflammation induce a reduction of striatal DA that in turn leads to a steeper effort-discounting curve because of reduced perceived ability (can't) versus preference (won't) for reward. This theoretical framework can inform how the mesolimbic DA system responds to increased immunometabolic demands during chronic inflammation, ultimately contributing to motivational impairments in psychiatric and other medical disorders.

Highlights

Converging evidence suggests that the mesolimbic dopamine (DA) system is directly affected by increases in inflammatory cytokines associated with chronic, low-grade inflammation.

The reasons for this immune–DA communication are unclear, but one novel hypothesis is that inflammatory cytokines signal immunometabolic shifts that impact the valuation of future actions as a function of available energy resources.

Future work on effort-based discounting models should incorporate variables related to inflammation and immunometabolic state.

Dopamine, Effort, and the Inflammatory Response

The efficient utilization of energy resources for goal-directed behaviors is believed to have been a driving force in the evolutionary development of the central nervous system (CNS) and its response to the environment [1]. Over the past several decades, our understanding of the neurobiological mechanisms that govern exploratory behavior and goal pursuit has expanded exponentially. This work has revealed a central role for mesolimbic signaling of the phylogenetically conserved neurotransmitter dopamine (DA) in shaping willingness to expend energy [2–5] or forage [6–8] and the drive to overcome obstacles [9,10] in pursuit of rewards. To date, however, the majority of studies have focused on the behavioral consequences of mesolimbic DA signaling within the striatal, limbic, and cortical areas that mediate various aspects of normal and abnormal reward-seeking behavior. By contrast, a smaller body of work has focused on inputs to the mesolimbic DAergic system from sources outside the CNS that communicate relevant bodily states to influence the responsivity of DAergic neurons and the calculus of effort-based decision-making.

One emerging source of this external regulation is inflammation. There is growing appreciation that many of the behavioral sequelae associated with infection and the related inflammatory response, including alterations in reward-seeking behavior (as occurs in so-called 'sickness behavior'), are a direct consequence of the impact of inflammatory cytokines on mesolimbic DA signaling [11,12]. To date, however, the broader implications of this mesolimbic DA–immune axis have yet to be fully explored. Herein, we propose that inflammatory signaling molecules play a critical role in communicating information relevant to shifts in immunometabolism that impact available energy resources in the body – a prerequisite for the mesolimbic DA system to generate accurate estimates of expected value of reward and guide effort allocation and energy expenditure. This function may have originated during evolution as a means of suppressing exploratory behavior and shifting energy resources to the immune system for fighting infection and healing wounds in an ancestral environment rife with pathogens and predators [13,14]. Nevertheless, we suggest that, in the modern world, communication between the immune

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system and DA may be crucial in shaping effort allocation as a function of peripheral immunometabolic states characterized by the increased energy demands of chronic low-grade (nonresolving) inflammation. Such states include chronic stress, obesity, the metabolic syndrome, aging, dysbiosis, and a variety of medical illnesses and their treatments [15,16].

The overarching goals of this review are: first, to summarize the extant body of research describing the impact of inflammatory mediators on mesolimbic DA signaling; next, to review the metabolic consequences of chronic inflammation; and finally, to integrate these two literatures into a comprehensive framework to account for the effects of inflammation and its attendant immunometabolic costs on effort discounting. As part of this framework, we adapt an established computational model of effort discounting to incorporate the effects of chronic inflammation on energy availability. This model provides the basis for indexing and calculating the effects of chronic inflammation and associated immunometabolic states on effort-based decision-making. We also touch on the implications of this mesolimbic DA–immune axis for understanding impairments in motivated behavior in psychiatric disorders, such as depression and schizophrenia, along with potential translational implications.

Inflammation and Dopaminergic Drive

Overwhelming evidence suggests that a primary function of the mesolimbic DA system is to determine motivational drive; that is, the value of investing effort in the pursuit of rewards [9,17–19]. In animal models this has been demonstrated convincingly via experimental manipulations including pharmacological blockade of DA transmission [9,17] and optogenetic manipulation of DA neurons [19] as well as correlative studies showing that striatal DA release exhibits a 'ramping' signal that approximates reward availability [20,21]. Effort-based decision-making paradigms that operationalize motivation by assessing an individual's willingness to invest greater effort to obtain larger or preferred rewards have repeatedly demonstrated that DA is both necessary and sufficient for motivated behavior [9,22]. In addition, potentiation or attenuation of DA signaling can increase or decrease effort expenditure for rewards in both rodents [3,4,23] and humans [5,24]. Of note, these actions of the DA system are somewhat distinct from reward prediction error (RPE) encoding [25,26], a discussion of which is beyond the scope of this review (see [18,27] for reviews). Nevertheless, data suggest that striatal DA release may be distinct from midbrain DAergic neuron firing rates [20] and serves primarily to signal the need for action [19,28,29], consistent with the interpretation that striatal DA reflects the expected value of work [18,19].

Based on the role of mesolimbic DA in effort expenditure for reward and reward valuation, inputs to the DA system from the peripheral body are essential to accurately estimate prevailing needs and energy resources for effort expenditure. While there are several mechanisms that have been studied relevant to peripheral inputs, including those related to hunger and thirst (Box 1), growing attention is being paid to the impact of inflammation on DA signaling and its potential implications for reward-seeking behavior. Inflammatory cytokines have been shown to disrupt DA neurotransmission including DA synthesis, release, and reuptake in multiple experimental systems including laboratory animals and humans [30–34] (Table 1).

Some of the first data supporting the notion that inflammation may influence DA pathways came from studies using positron emission tomography (PET) to examine glucose metabolism in the brain of patients receiving the inflammatory cytokine interferon (IFN)-α for either malignant melanoma or hepatitis C [35,36]. These studies revealed evidence of increased glucose metabolism in subcortical regions consistent with changes observed in Parkinson's disease (PD). Further supporting the idea that inflammation may target DA signaling, administration of