OREXIN

Stay alert, don't get hurt

Both nucleus accumbens and orexin play clear roles in motivated behavior, but the functions of orexin projections to accumbens are poorly understood. Blomeley et al. show that this pathway, via specific orexin excitation of dopamine D2 receptor–expressing neurons, can inhibit reward seeking and exploratory drive when danger is perceived.

Stephen V. Mahler

In a dangerous world, we must attain the necessities of life but also stay vigilant for potential harms. Indeed, navigating this balance is one of the most fundamental functions of the brain. Blomeley et al.[1] show that the decision to play it safe is mediated, in part, by a tiny cluster of a few thousand neurons expressing the neuropeptide orexin (also called hypocretin) that are exclusively present in a restricted region of the hypothalamus. These neurons play wide-ranging roles in so-called motivational activation, coordinating wide-ranging behavioral and physiological responses when key fitness-related situations are encountered[2].

Neurons expressing orexin, via their widespread projections throughout the brain, are essential both for highly motivated pursuit of natural and drug rewards and for responses to acute stressors. Blomeley et al.[1] add an important new piece to this puzzle regarding orexin's role in motivation. They show that orexin neurons also mediate avoidance of risk, via a previously undescribed and remarkably selective projection to a subset of neurons in the nucleus accumbens. This lends new insight into how orexin neurons not only facilitate motivation to act, but also inhibit behavior in service of avoiding danger. In other words, these neurons promote an even wider range of survival strategies than previously expected.

In the life of a mouse, avoiding predation is a crucial evolved drive that must always be considered when deciding what to do and what not to do. The authors synthesize the known roles of orexin in coordinating specific adaptive behavioral programs[2] and the potential role of 'indirect pathway' striatal medium spiny neurons (MSNs) expressing the dopamine D2 receptor in inhibiting actions[3]. In dorsal striatum, D2- and D1-expressing MSNs are interspersed and, via their differential projections to globus pallidus interna (the D2-expressing indirect pathway) or substantia nigra (the D1-expressing direct pathway), inhibit or promote actions, respectively. In this way, dopamine can both promote (via excitatory D1 receptors) and inhibit (via inhibitory D2 receptors) activity of the MSN populations, thereby helping select amongst competing behavioral plans represented by these populations and their differential outputs to thalamocortical motor pathways.

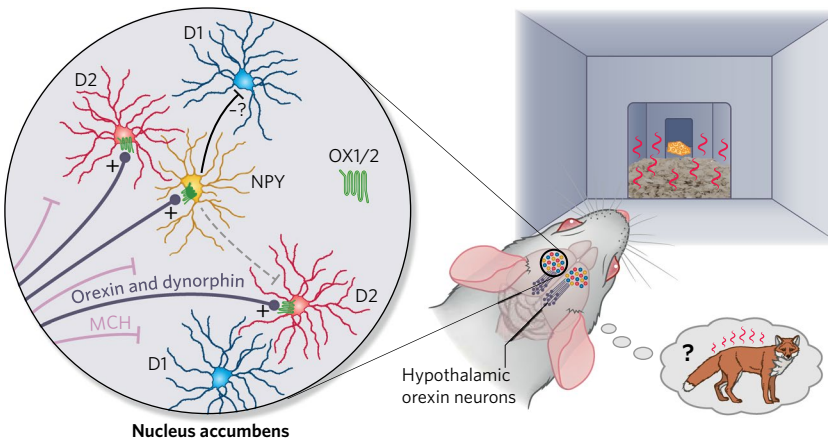

Fig. 1 | An orexinergic input to nucleus accumbens that promotes risk avoidance. Hypothalamic orexin (but not melanocortin concentrating hormone, MCH) neuron projections to nucleus accumbens excite D2-expressing indirect-pathway MSNs, which may inhibit specific action plans in favor of others. Here this pathway promotes avoidance of risky situations such as crossing a predator-scented chamber to attain food. D1-expressing accumbens MSNs are not similarly excited by orexin, though neuropeptide Y (NPY) interneurons are, showing the remarkable anatomical and functional specificity of this pathway. Credit: Debbie Maizels/Nature Publishing Group.

The authors now show a mechanism by which orexin neurons control MSN populations in nucleus accumbens, a key aspect of the ventral striatum. Specifically, they find that orexin projections to accumbens selectively target and excite D2-expressing MSNs, thereby inhibiting risky behaviors such as venturing into the potentially dangerous center of an open field or crossing, in pursuit of reward, a portion of a chamber scented with the odor of a predator (Fig. 1). Orexin, through actions at orexin 1 and/or 2 (OX1/2) receptors, excites D2-expressing accumbens MSNs, while it does not excite D1 expressing MSNs. They also show that orexin robustly excites neuropeptide Y interneurons in accumbens (these neurons also contain somatostatin and nitric oxide synthase, and they are sometimes called persistent and low-threshold spike neurons), which strongly inhibit MSNs[4]. Potentially, these neurons could inhibit D1 MSNs while orexin directly excites D2-expressing ones, decreasing the likelihood of making a risky move. If so, this means orexin can inhibit risky action plans by stimulating D2-expressing MSNs while simultaneously (indirectly) inhibiting D1 MSNs that would facilitate such actions, a possibility that should be tested directly in future studies. The authors demonstrate the specific anatomical characteristics and behavioral functions of the orexin→D2 MSN pathway using a combination of slice electrophysiology, opto- and chemogenetic

manipulations, and rabies-assisted tracing of monosynaptic connectivity between orexin and D2 neurons. In contrast, the parallel projection from an interspersed hypothalamic population of neurons expressing melanocortin concentrating hormone to striatum does not similarly target or excite D2-expressing accumbens MSNs, showing marked specificity in the connectivity between these important motivation-related hypothalamic and striatal populations.

Surprisingly little was previously known about the functions of orexin projections to accumbens, despite the presence of orexin receptors there and the presence of dense orexin-expressing axons in the dorsomedial accumbens shell[5,6]. Several reports show a role for this pathway in motivation, hedonics and arousal[7,8], but none have examined how it affects functionally opposed MSN subpopulations. The present report is likely to make a large impact on those studying striatal MSN circuits or the motivational functions of either accumbens or orexin. However, it is hard to understand how these findings relate to prior reports showing that almost 80% of accumbens neurons are excited by orexin[9], while D2 neurons there represent less than half of the MSN population[10]. In addition, dopamine plays overlapping roles with orexin in appetitive motivation[2], and washing dopamine onto ex vivo accumbens shell brain slices excites many of the same accumbens cells (presumably D1-expressing MSNs) that are excited by orexin B peptide (here shown to be D2 MSNs)[9]. This implies additional complexity in the physiological and behavioral functions of orexin inputs to accumbens core and/or shell that is still obscure and that should be further investigated in light of these intriguing new data.

This report also highlights several other areas in which more research is sorely needed to understand this complex circuit. First, the impact of circadian oscillations in orexin signaling is untested, as all experiments here were performed in the resting (light) phase of the day, when nocturnal rodents spend most of their time sleeping and when central orexin neuron levels are low[11]. An examination of how this newly discovered pathway functions in the context of greater basal orexin levels in the active phase is therefore needed.

Another unanswered question brought up by these data regards the role of dynorphin, an endogenous opioid peptide that is expressed in nearly 100% of orexin neurons[12]. Dynorphin, via actions at kappa opioid receptors in accumbens and elsewhere, is well-known to promote aversion, and upregulation of kappa signaling in accumbens is associated with depression-like phenotypes[13]. Kappa receptors modulate activity of both D1 and D2 neurons in accumbens[14], and dynorphin is co-released with orexin, at least in the ventral tegmental area[15]. This begs the question of how accumbens dynorphin and orexin co-release might interact to influence activity of these MSN subpopulations, modulating neural activity and risk avoidance or other motivated behaviors.

These data also hint that orexin modulation of accumbens MSN subpopulations may be more complex than suggested. The authors show that chemogenetic inhibition of D2 MSNs strongly inhibits risk avoidance, as does (to a lesser extent) blocking orexin signaling at the OX1 receptor with intra-accumbens SB334867. However, when D2 neurons were inhibited while orexin was locally antagonized, only partial inhibition of risk avoidance was observed, equivalent to effects of blocking orexin alone. This implies that a more complex interaction between orexin and D2 neuron activity may exist than is characterized here. Potentially, this finding could result from inhibition of aversion-specific functions of accumbens orexin that compete with the peptide's newly discovered role in risk avoidance. However, orexin in accumbens promotes seeking of drug and natural rewards, as well as activity more generally[8], and inhibiting such effects would be expected to facilitate the behaviors here defined as risk avoidance: namely, hesitation to explore or to retrieve a reward. It is possible that this puzzling finding instead involves OX2 receptors, which are more robustly expressed than OX1 in accumbens and which were presumably not blocked by SB334867 in behavioral experiments (though both OX1 and OX2 were blocked in physiology experiments, where sedative effects of OX2 antagonism were not a concern). Complex interactions with dynorphin co-release from orexin neurons could also be relevant here, since dynorphin activity would be expected to remain intact after pharmacological orexin blockade. Alternatively, this finding could result from a complex and poorly characterized interaction of orexin effects on D1 and D2 MSNs, as well as neuropeptide Y interneurons or other interneurons that control MSNs. The present findings will likely spur interest in further exploring these possibilities or other potential mechanisms by which orexin neurons control ventral striatal MSN populations.

Like most important papers, this one poses as many questions as it answers. It is likely that unraveling the complex interactions between hypothalamic orexin and ventral striatal MSN subpopulations will keep researchers interested in the motivation and motor functions of hypothalamic–striatal interactions busy for years to come. ❐

Stephen V. Mahler

Department of Neurobiology & Behavior, University of California, Irvine, Irvine, CA, USA.
e-mail: mahlers@uci.edu

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Competing interests

The author declares no competing financial interests.