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A Circuit Perspective on State-Dependent Effects of Dopamine Stimulants

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Drugs often target multiple neuronal types. Thus, their behavioral effects may vary according to brain-state-dependent inter-neuronal interactions. In this issue of *Neuron*, Alhadeff et al. (2019) document hunger and dopamine-dependent alcohol effects, revealing specific circuit-level determinants of variable drug outcomes.

Behavioral effects of recreational drugs can be notoriously variable within and between individuals. For example, alcohol has been documented to have either stimulatory or sedative behavioral effects (Hendler et al., 2013). Many underlying causes have been proposed, such as variations in drug metabolism or distinct dose-responses of different outcomes. Recreational drugs are typically not selective for one cell type but alter the activity at multiple sites in brain networks. For example, alcohol alters neuronal electrical excitability by acting on molecular targets throughout the brain (Crews et al., 1996). The signal propagation (functional connectivity) between brain network nodes is often directed (asymmetric) and depends on the interaction of pre- and postsynaptic activity with synaptic strength (Bassett and Sporns, 2017). These fundamental features of brain networks suggest that when drugs interact with multiple neurons, this non-specific action can still be converted into specific (but variable) effects at the system level, in a way that depends on the network connectivity state (Figure 1A). Here, we discuss how this theoretical perspective may relate to some recent experimental evidence. Using alcohol and food intake as examples, we propose a specific neurochemical and circuit explanation that may contribute to variable effects of a broad class of dopamine-stimulating drugs.

Alcohol (ethanol) has been variously reported to inhibit (Alhadeff et al., 2019), stimulate (Cains et al., 2017; Yeomans, 2010), or have no effect on (Alhadeff et al., 2019) food intake. It has also been demonstrated to either stimulate (Cains et al., 2017; Cubero et al., 2010) or inhibit (Alhadeff et al., 2019) hypothalamic agouti-related peptide (AgRP) neurons, a key node in brain networks that senses nutrient deficit and promotes homeostatic eating (Sternson, 2013). While this variation may in theory arise through experimental paradigm differences, or through general mechanisms depicted in Figures 1A and 1B, specific experimental examples have proven elusive. The study of Alhadeff et al. (2019) in this issue of *Neuron* now provides such an example by demonstrating interdependencies between ethanol effects, hunger state, and dopaminergic influence on hypothalamic feeding circuits (Alhadeff et al., 2019). They found that ethanol inhibits food intake in food-restricted, but not in *ad lib* fed, mice (Alhadeff et al., 2019). In fed mice, ethanol had some tendency to increase food intake (e.g., Figure 4A, 5% ethanol, of Alhadeff et al., 2019), but this did not reach significance. In hungry mice, ethanol inhibited AgRP neurons and food intake (Alhadeff et al., 2019). The effect of intragastric ethanol on AgRP neurons was unaffected by destruction of the vagus nerve, but it was suppressed by dopamine receptor antagonists (Alhadeff et al., 2019), supporting the idea that ethanol is not sensed as calories peripherally but directly acts on the brain. This suggests that inhibitory effects of ethanol on AgRP neurons and eating may rely, at least in part, on ethanol-induced dopaminergic inhibition of AgRP neurons.

Why does ethanol inhibit eating in hungry but not satiated mice? Interestingly, phasic dopamine signaling is enhanced in hunger, for example as manifested in hunger-potentiated dopamine responses to food cues (Volkow et al., 2011). Ethanol stimulates dopamine neurons and increases dopamine release (Alhadeff et al., 2019). We therefore propose that hunger-induced dopamine sensitization (Volkow et al., 2011) could also augment the dopaminergic component of neural circuit modulation by drugs (Figure 1C). Therefore, hunger-induced dopamine sensitization may make dopamine-dependent effects of alcohol (such as AgRP cell inhibition, Alhadeff et al., 2019) more dominant. This dopamine-driven AgRP cell inhibition would uncouple eating from homeostatic needs. Conversely, during satiety, the dopaminergic effects of ethanol would become less dominant, perhaps allowing other neural effects of ethanol (Cains et al., 2017; Crews et al., 1996) to influence local circuitry and overall behavior. Drugs whose cellular outcomes include dopaminergic stimulation—such as cocaine, amphetamine, and nicotine—all inhibit AgRP neurons in food-restricted mice (Alhadeff et al., 2019). Thus, we speculate that the outcomes of any dopamine stimulants may also be hunger-dependent, due to the hunger-induced dopamine sensitization described above (Figure 1C).

The hunger-induced dopamine sensitization—which at cellular and systems levels may be caused by increased synaptic dopamine content, postsynaptic receptors, and/or AgRP neuron activity—provides an explanation for why effects of dopamine-influencing drugs may vary with hunger state. This explanation is appealing because it unifies contradictory observations on variable behavioral effects of drugs by relating them to literature on hunger-dependent dopaminergic

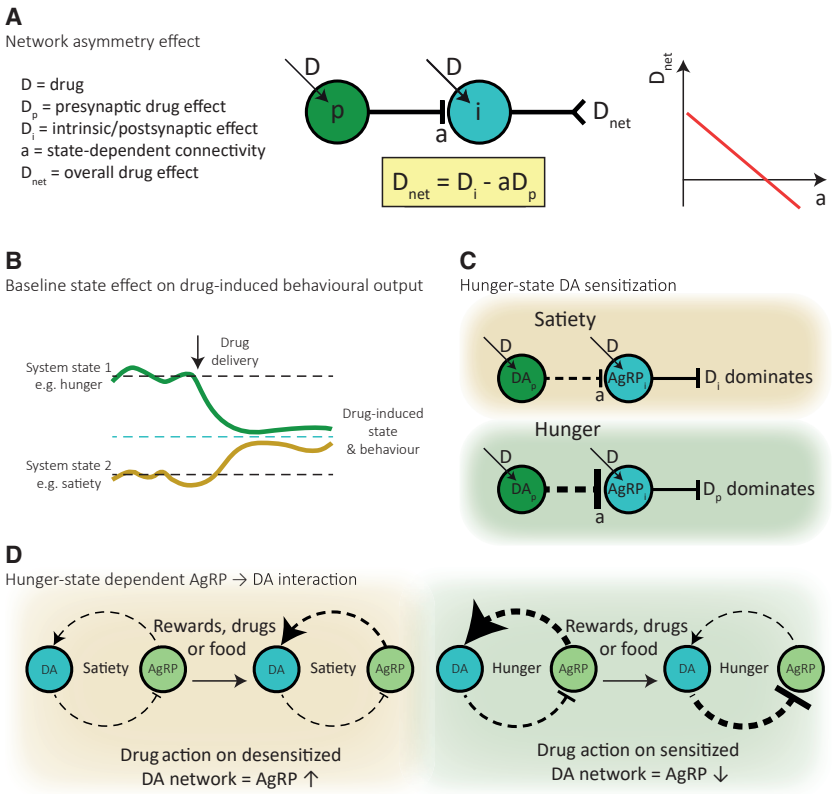

Figure 1. Influence of Dynamic Circuit and System States on Variable Effects of Drugs

(A) Circuit consisting of a single inhibitory synapse is sufficient to convert non-specific drug action into a specific drug output (center), while variability in synaptic strength is sufficient to change the direction of the net drug effect (right). In the center plot, T-bar is inhibition, and Y-bar is activation.

(B) Variable system state baseline, consisting of combined activity states and synaptic strength, can determine whether the drug increases or reduces the state relative to baseline.

(C) Theoretical application of the principle in (A) to the interaction of presynaptic dopamine effects (DA_p) with intrinsic excitability of AgRP neurons ($AgRP_i$) in hunger and satiety states, illustrating how hunger-induced dopamine sensitization (i.e. increased synaptic weight, "a"-labeled bar) shifts the net drug output toward presynaptic influence.

(D) AgRP neurons themselves may increase cue or drug-dependent dopamine signaling (as demonstrated by Alhadeff et al.), thus partially explaining the feeding-state dependence of drug-induced effects on AgRP and dopamine systems.

connectivity (Volkow et al., 2011). However, many questions remain to be clarified to assess when this circuit mechanism is active. For example, is there a difference in the amplitude of dopamine-stimulant-induced AgRP neuron inhibition between hunger and satiety, and is this difference dopamine dependent? Where might dopamine input to AgRP neurons come from? What is the mechanism of dopamine sensitization as it relates to AgRP neurons; for example, do these neurons express different types of dopamine receptors in a hunger-dependent manner, and is this altered by alcohol? How is brain ethanol concentration affected by fasting-affected variables, such as gastric emptying and alcohol dehydrogenase levels? Given that alcohol is a calorie-dense nutrient, where do the calories go in experiments where mice don't gain weight and don't change food intake during chronic alcohol administration (Alhadeff et al., 2019)? Are other neuronal populations responsible for energy homeostasis also affected by dopamine stimulants? Alhadeff et al. (2019) show that AgRP cell stimulation increases dopamine output; therefore, do AgRP neurons mediate hunger-induced dopamine sensitization? This would suggest that hunger sensitizes dopamine signaling via hyperactive AgRP neurons, which in turn results in greater inhibition of AgRP neurons by dopamine stimulators such as drugs, food, or potentially other rewards (Figure 1D).

In summary, a state-dependent global neurocircuit perspective may improve prediction, and rationalize seemingly contradictory observations, of drug outcomes. Specifically, homeostatic states such as hunger may dramatically change global brain circuit state and thus drug effects. Experimental tools for observation of brain-wide neurocircuit dynamics are becoming available (e.g., Allen et al., 2019), and their application to drug studies would advance understanding of how drugs combine with states of mind to alter behavior.

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