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Lack of inhibition leads to abuse

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Abstract

Chronic drug use can lead to addiction, which is initiated by specific brain circuits. The mystery of how one class of drugs, the benzodiazepines, affects activity in this circuitry has finally been solved.

Common illnesses such as anxiety disorders, insomnia and even muscle spasms are treated with benzodiazepine drugs, of which diazepam (Valium) is perhaps the best known. But both conventional benzodiazepines and newer benzodiazepine-like compounds (such as zolpidem) are addictive. This limits the therapeutic potential of an otherwise safe class of drugs that has broad clinical applications.

Most addictive substances activate the same brain circuitry: the dopaminergic system, which is also stimulated by natural rewards, such as food and sex. Benzodiazepines stimulate this circuitry, but the underlying mechanism was unknown, prompting speculation that benzodiazepine addiction involves systems distinct from those involved in dependence on other addictive drugs.

In this issue (page 769), Tan *et al.*¹ report that the missing link connecting benzodiazepines to the dopaminergic circuitry is a select group of GABA_A receptors (γ -aminobutyric acid type A receptors) that reside on neurons known as inhibitory interneurons. These interneurons coordinate the output of dopaminergic neurons in the ventral tegmental area (VTA) of the brain. GABA_A receptors are assembled from five subunits, of which there are several types; the authors find that, in inhibitory interneurons, benzodiazepines increase the stimulation of GABA_A receptors that contain $\alpha 1$ subunits. This reduces activity in the interneurons and thereby increases excitability in VTA dopaminergic cells. Through a series of ingenious experiments, Tan *et al.* demonstrate that this mechanism contributes to benzodiazepine addiction.

In general, the urge to self-administer an addictive drug is initiated in the VTA by the ‘strengthening’ of excitatory glutamatergic synapses — neural junctions at which glutamate is the primary neurotransmitter — to dopaminergic neurons. Such strengthening increases the chance that the synapse will release glutamate and is caused by the recruitment of new AMPA receptors (a class of glutamate receptor) to glutamatergic synapses on dopaminergic neurons. In agreement with an earlier study², Tan *et al.*¹ found that benzodiazepines also cause this effect in mice, regardless of whether the drugs are injected systemically (whereupon they can interact with GABA_A receptors throughout the animal’s body) or directly infused into the VTA.

The authors obtained similar results with zolpidem, which binds predominantly to GABA_A receptors that contain $\alpha 1$ subunits. But they detected no such strengthening in wildtype mice in which a benzodiazepine was co-administered with a compound that blocks the benzodiazepine binding site on GABA_A receptors (a benzodiazepine antagonist), or in mice that were genetically engineered so that their $\alpha 1$ subunits were unable to bind benzodiazepines. Taken together, these results showed that the cellular changes that occur in dopaminergic neurons after a single exposure to benzodiazepines require functional $\alpha 1$ subunits in GABA_A receptors.

Tan *et al.* then mapped the location of $\alpha 1$ -containing GABA_A receptors within the VTA's microcircuitry, and found that the highest density was not on dopaminergic cells, but on the inhibitory interneurons — the same class of cells targeted by opioid drugs such as morphine³. In fact, much of morphine's addictive potential is attributed to the inhibition of these interneurons in the VTA.

To better understand commonalities between benzodiazepines and opioids, the authors¹ treated $\alpha 1$ -mutated mice with morphine. Surprisingly, they observed that morphine caused the cellular changes normally associated with benzodiazepines — the recruitment of new AMPA receptors to glutamatergic synapses on dopaminergic neurons. This result suggested that, despite differences in their binding sites, benzodiazepines and opioids ultimately share the same interneuron target. The authors therefore reasoned that benzodiazepines, like opioids, might increase the excitability of dopaminergic neurons by reducing interneuron-mediated inhibition, a process known as disinhibition.

Tan *et al.* tested this theory by sampling VTA dopaminergic cells from brain slices and recording the inhibitory currents mediated by GABA_A receptors in these cells. In tissue from wild-type mice, they observed that a typical benzodiazepine (midazolam) reduced the inhibitory current in dopaminergic neurons, in line with the disinhibition hypothesis. Conversely, in $\alpha 1$ -mutated mice, the inhibitory currents in dopaminergic cells increased in response to the drug, suggesting that benzodiazepines reduce the release of GABA in wild-type mice.

The authors went on to record the activity of VTA neurons *in vivo*, and noted that, in wild-type mice, benzodiazepines simultaneously activated dopaminergic neurons and inhibited GABAergic interneurons. This disinhibition effect was reversed when the authors subsequently administered a benzodiazepine antagonist to the animals. What's more, disinhibition was altogether absent in $\alpha 1$ -mutated mice.

Finally, the researchers studied how prone their mice were to self-administering benzodiazepines. When given a choice between drinking either a sugar solution or a sugar solution laced with midazolam, wild-type mice preferred the midazolam-containing solution. The $\alpha 1$ -mutated mice, however, showed no such preference, even though they drank as much liquid overall as the wild-type animals, and preferred sugar solution to pure water (indicating that they were capable of reward-motivated discrimination).

Taken together, Tan and colleagues' data¹ suggest that the activation of $\alpha 1$ -containing GABA_A receptors by benzodiazepines calms GABAergic interneurons, reducing their

overall inhibitory output. Consequently, dopaminergic neuron firing increases in the VTA, which elevates the number of AMPA receptors in the membranes of the excited dopaminergic neurons and strengthens the excitatory synapses that favour addiction (Fig. 1). This general disinhibition mechanism is analogous to that involved in opioid drug abuse³.

More studies are required to fully appreciate the context of the proposed mechanism¹. For example, synaptic scaling — a homeostatic process that adjusts the strength of a neuron's excitatory synapses up or down to stabilize firing^{4,5} — also modulates the number of AMPA receptors in neuron membranes, but its relevance in the VTA isn't clear and will be challenging to determine. Another consideration is that both dopaminergic and GABAergic cells receive GABAergic innervation, and the distribution of $\alpha 1$ -containing GABA_A receptors in these systems is both presynaptic and postsynaptic. This somewhat ambiguous distribution suggests that additional $\alpha 1$ -dependent mechanisms of addiction might exist in which benzodiazepines modulate the excitability of dopaminergic cells.

Other findings indicate that benzodiazepine abuse is not always attributable to $\alpha 1$ -containing GABA_A receptors. For example, it is unclear why the overall incidence of zolpidem addiction is low relative to that of less-selective benzodiazepines (those that, unlike zolpidem, show no binding preference for $\alpha 1$ GABA subtypes), opioids or other drugs of abuse⁶. It is also unclear why primates will self-administer⁷ a benzodiazepine known as L-838 417, which binds to, but does not activate, $\alpha 1$ -containing GABA_A receptors and (as Tan *et al.*¹ show) does not change AMPA-receptor distribution in dopaminergic neurons.

Nevertheless, Tan and colleagues' discovery¹ is a landmark for the field — these authors are the first to identify a molecular mechanism contributing to benzodiazepine abuse. Given that the $\alpha 1$ subunits of GABA_A receptors are not responsible for the therapeutic effects of benzodiazepines⁸, the work highlights an exciting possibility: if benzodiazepines can be designed that lack affinity for this subunit, then the addictive properties of these versatile and useful drugs might be reduced.

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Figure 1 |. Proposed mechanism of addiction of benzodiazepine drugs.

Tan *et al.*¹ report that benzodiazepine drugs bind to and activate certain GABA_A receptors (γ -aminobutyric acid type A receptors) — those that contain $\alpha 1$ subunits — on interneuron cells in the ventral tegmental area (VTA) of the brain. **a**, These interneurons ordinarily inhibit the activity of dopaminergic neurons in the VTA. Forked branches are synapses (neural junctions). **b**, Activation of the GABA_A receptors by benzodiazepines reduces the amount of inhibition (a process known as disinhibition, red cross), which increases the activity of the VTA's dopaminergic neurons. This increased activity strengthens the VTA's glutamatergic synapses (neural junctions at which the primary neurotransmitter is glutamate) to dopaminergic neurons, making them more excitable. Such strengthening, caused by an increase in the number of glutamate receptors on the dopaminergic neuron, is the cellular response to natural rewards (such as food), but it also forms the basis of the addictive properties of drugs