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Epigenetic tinkering with neurotransmitters

Some neurotransmitters are used to modify chromatin and modulate gene expression

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Dopamine is a monoamine neurotransmitter associated with movement and reward responses. The ventral tegmental area (VTA), a tiny midbrain region involved in motivation and addiction, and the neighboring substantia nigra contain most brain dopamine neurons. Dopamine neurons encode reward prediction errors (1, 2), and dopamine conveys motivational value and promotes movement at multiple time scales (3). VTA dopamine neurons are part of the brain reward circuit. A central action of addictive drugs and addictive behaviors, such as gambling, is to increase extracellular dopamine in the regions innervated by these neurons, such as the nucleus accumbens (4). It therefore comes as a surprise that dopamine is also an epigenetic mark. On page xxx of this issue, Lepack et al. (5) show that covalent attachment of dopamine (dopaminylation) to histone H3 glutamine 5 (H3Q5dop) plays a role in cocaine-induced transcriptional plasticity. Reducing dopaminylation prevented withdrawal-induced changes in gene expression and reduced cocaine-seeking behavior in rats.

The existence of protein modification by a monoamine neurotransmitter was initially shown to occur in platelets (6, 7). In stimulated platelets, serotonylation of fibrinogen and small guanosine triphosphatases (GTPases) facilitates platelet adhesion and blood clot formation. Several other intracellular and extracellular proteins are serotonylated during diverse biological responses, including cytoskeleton and spine remodeling, muscle contraction, insulin secretion, and serotonin transporter translocation (8). The transfer of serotonin to the side chain of a glutamine residue is catalyzed by tissue transglutaminase 2 (TGM2). This is a ubiquitous member of the transglutaminase family, present inside and outside of cells, and it is also a key antigen in celiac disease, which is a gluten-associated autoimmune disease (9, 10). TGM2 cross-links proteins and covalently couples primary amines to a peptide-bound glutamine residue, a reaction called aminylation (7).

It was recently discovered that histone H3 glutamine 5 serotonylation (H3Q5ser) occurs in the brain and gut of diverse organisms that are capable of producing serotonin (11). This modification also occurs when the neighboring residue, lysine 4 (K4), is trimethylated (H3K4me3), a modification associated with transcriptional initiation (12). Serotonylation in vivo only occurs with concomitant trimethylation of the adjoining amino acid residue (11). During differentiation of serotonin neurons from human pluripotent stem cells, this dual modification (H3K4me3Q5ser) is enriched at active gene promoters and correlates with increased gene expression (11). This suggests that H3K4me3Q5ser is an epigenetic mark that is permissive for transcription during differentiation of serotonergic neurons. Indeed, doubly modified histone H3 enhances binding of the general transcription factor IID (TFIID) to H3K4me3 (11, 12) (see the figure).

Lepack et al. found that histone H3 dopaminylation in VTA neurons results from TGM2 activity. In the postmortem VTA of cocaine users, H3Q5dop concentrations were decreased. In rats self-administering cocaine during 10 days with extended access to the drug, H3Q5dop initially decreased, as in the case of human users whose brains contained cocaine at the time of death. Yet in these rats, after a month of cocaine withdrawal, H3Q5dop was higher than in controls. Extended self-administration of cocaine was necessary for the H3Q5dop biphasic change to occur, because neither restricted self-administration nor passive administration of cocaine nor self-administration of food had any effect, suggesting a specific regulatory mechanism.

To test the function of H3Q5dop, Lepack et al. used viral overexpression of a histone H3 variant (H3.3) in which glutamine 5 was replaced by an alanine residue, preventing dopaminylation. In rats expressing mutated H3.3 in the VTA before the 30-day cocaine withdrawal, changes in gene expression were reduced, supporting a permissive epigenetic role of H3Q5dop. The firing rate of VTA dopamine neurons from these rats was decreased, and they released less dopamine in the nucleus accumbens. Prevention of H3Q5dop in the VTA also selectively decreased the drug-seeking behavior of rats trained to self-administer cocaine, without altering other behaviors. These results suggest that H3Q5dop plays a role in the transcriptional alterations that underlie neuronal and circuit adaptations leading to drug seeking. The downstream effects of H3Q5dop are unknown. They could be similar to those of serotonylation and facilitate transcription by enhancing H3K4me3 interactions with TFIID or other transcription factors. However, H3Q5dop and H3K4me3 were at least partly dissociated *in vivo*, and the chemical differences between the seronyl and dopaminylation moieties may have different consequences for histone interactions.

The use of the same monoamine molecule as a neurotransmitter and a histone modification in the same cells illustrates that evolution proceeds by molecular tinkering, using available odds and ends to make innovations (13). These findings also raise exciting questions for future research. It is unclear what regulates serotonylation and dopaminylation and their removal from histone H3. Because TGM2 concentrations are regulated and its activity is calcium (Ca²⁺) dependent (9, 10), it will be important to examine the role of synaptic and neuronal activity. What is the role of substrate availability? It is unclear whether changes in intranuclear concentration of dopamine or serotonin matter. Cocaine increases extracellular concentrations of dopamine by blocking the dopamine transporter, but the subsequent changes in intracellular dopamine concentration in VTA neurons are not known. A decrease due to reuptake inhibition could hypothetically decrease dopaminylation after cocaine self-administration. However, it would be expected to also occur when rats received cocaine passively, suggesting the existence of more integrated regulation. It will also be interesting to examine the effects of antidepressant drugs on serotonylation. Is there a role of H3K5ser in the delayed clinical effects of these drugs that act by preventing serotonin reuptake or degradation? Additionally, the similarities and differences of dopaminylation and serotonylation effects on epigenetic regulation are important to understand. Future work will tell whether aminylation of H3Q5 is a curious and isolated epigenetic modification limited to a single histone residue in monoamine-rich cells or whether it is a more general mechanism.

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