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Review

Signals from the Fourth Dimension Regulate Drug Relapse

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Despite the enormous societal burden of alcohol and drug addiction and abundant research describing drug-induced maladaptive synaptic plasticity, there are few effective strategies for treating substance use disorders. Recent awareness that synaptic plasticity involves astroglia and the extracellular matrix is revealing new possibilities for understanding and treating addiction. We first review constitutive corticostriatal adaptations that are elicited by and shared between all abused drugs from the perspective of tetrapartite synapses, and integrate recent discoveries regarding cell type-specificity in striatal neurons. Next, we describe recent discoveries that drug-seeking is associated with transient synaptic plasticity that requires all four synaptic elements and is shared across drug classes. Finally, we prognosticate how considering tetrapartite synapses can provide new treatment strategies for addiction.

Trends

Drug-induced plasticity involves all aspects of tetrapartite synapses.

Relapse involves common mechanisms that span multiple classes of abused drugs.

Tetrapartite synapses are novel targets for treating addiction.

The Fourth Dimension of Drug Addiction

Iconic synaptic connections between neurons consist of specialized morphology and patterned expression of proteins in both pre- and postsynaptic elements. The traditional bipartite synapse provides mechanisms for regulating transmitter release probability and grading postsynaptic responses through ionotropic receptor-mediated ion fluxes and metabotropic receptor intracellular signaling cascades. Excitatory glutamatergic synapses constitute a majority of synaptic contacts in the brain, and extensive research over the past 50 years provides deep understanding not only of signaling produced by acute transmitter release but also of how different stimulation patterns change synaptic efficacy by causing enduring changes in release probability and/or postsynaptic responses. Thus, **long-term potentiation** (**LTP**; see Glossary) and **long-term depression** (**LTD**) are canonical changes in synaptic efficacy whereby the brain codes environmental experiences, and links these experiences to both adaptive behaviors and the behavioral changes characterizing drug addiction [1].

Glia account for over 50% of all cells in the brain, and traditionally function as structural and metabolic support for neurons [2]. In 1999, Araque *et al.* coined the term 'tripartite' synapse to account for the emerging role of astroglia in contributing to bipartite synaptic neurotransmission [3]. Astroglial processes tightly ensheath many excitatory synaptic contacts, and the patterned expression of glial **excitatory amino acid transporter 2** (**EAAT2**) and EAAT1 near the synaptic cleft is crucial for eliminating synaptically released glutamate and maintaining the fidelity of synaptic transmission [4,5]. More recent studies reveal that astroglia can release neuroactive molecules and thereby regulate synaptic transmission, termed **gliotransmission**. Changes in glial protein expression and morphology accompany enduring synaptic plasticity [6–9], and accumulating data demonstrate that astroglia have an important role in dynamically regulating drug-induced structural and functional plasticity [10].

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The past 10–15 years have seen the gradual recognition that a fourth signaling domain plays a remarkable role in regulating synaptic transmission. Dityatev and colleagues proposed the term **tetrapartite synapse** in 2010 to include the proteinacious **extracellular matrix** (**ECM**) as a key fourth element [11]. The ECM surrounds all components of the tripartite synapse (Figure 1A) and binds to glial and neuronal membrane receptors via **cell adhesion molecules** (**CAMs**). Transmembrane CAMs, such as integrins, ephrins, and cadherins, play key roles in the development and maintenance of synapses and synaptic plasticity in the adult brain mediated via cell–cell and cell–ECM signaling cascades [12–15]. ECM proteins are secreted by both neurons and glia, which also release proteins that regulate ECM signaling via protein degradation [14,16,17], and, as first identified in 2002 by Kaczmarek and colleagues [18], catabolic activation of the ECM regulates dendritic spine morphology and synaptic plasticity in the mature CNS (see [14,17] for review). Key catabolic regulators of ECM signaling are the **matrix metalloproteases** (**MMPs**) that respond to synaptic activity and activate or inactivate proteins in the ECM [19]. Given the facts that the ECM thoroughly populates the extracellular space, and that the extracellular space accounts for ~20% of human neuropil volume [19,20], it is surprising that the ECM has been so slow to emerge as a crucial component of drug-induced synaptic plasticity. MMP degradation of the ECM was first implicated in addiction by Wright and colleagues in 2003 ([21]; reviewed in [17,22–24]), and in this review we highlight recent findings indicating that the deep focus on drug-induced synaptic plasticity in corticostriatal synapses needs to consider all four synaptic elements (Figure 2). In addition, embedded throughout this review is a comparison of the synaptic plasticity induced by different chemical classes of addictive drugs that allows us to explore the hypothesis that the molecular underpinnings of synaptic plasticity that are shared between classes of addictive drug are most relevant for treating shared symptoms of drug addiction, such as the persistent vulnerability to relapse. We further suggest that tetrapartite synaptic mechanisms of addiction may be a platform for integrating the relevant literatures generated for each drug class into a more unified understanding of the neurobiology of relapse to drug use.

Modeling Drug Addiction to Study Maladaptive Synaptic Plasticity

Research into the neurobiology of drug use generally focuses on two phases of the clinical syndrome. (i) Study of the transitory effects of acute drug administration and effects of early withdrawal from repeated drug use (see Box 1 for animal models used to provoke drug seeking). This strategy is most useful to understand the sequence of events that lead to the acquisition of drug dependence and compulsive drug-seeking behaviors. In general, research into the acquisition of drug-seeking behaviors has triangulated on shared involvement of drug-facilitated dopamine release and signaling in the development of drug-seeking behaviors across all chemical classes of addictive drug [25,26]. (ii) The second strategy is to study the long-lasting, constitutive changes in brain biology that underpin the enduring vulnerability to relapse. Akin to the 'common mechanism' status achieved by dopamine transmission as an essential component in developing drug-seeking behaviors, regardless of the class of addictive drug, in this review we propose that shared corticostriatal glutamatergic plasticity is a 'common mechanism' for all addictive drugs. Accordingly, we focus discussion on the second phase of the clinical syndrome, the constitutive synaptic plasticity that endures after many weeks of withdrawal and may underpin the enduring vulnerability to relapse. In addition, we introduce recent experiments studying a third phase of the clinical syndrome–the synaptic plasticity accompanying the execution of drug-seeking behavior that is initiated by drug-associated contexts and cues.

Drug Withdrawal and Constitutive Corticostriatal Synaptic Plasticity

Presynaptic and Astroglial Constitutive Plasticity

Among the earliest observations regarding enduring shared adaptations in corticostriatal synapses is drug-induced downregulation of signaling through $mGlu_{2/3}$ presynaptic inhibitory

Glossary

Cell adhesion molecules (CAMs): cell surface proteins that bind to ECM proteins and intracellular signaling systems that regulate synaptic function and morphology.
Chondroitin sulfate proteoglycans (CSPGs): proteoglycans that provide structural support and stabilize the ECM.
Chondroitinase ABC (ChABC): an enzyme that degrades the glycosaminoglycan component of chondroitin sulfate proteoglycans.
Constitutive synaptic potentiation (c-SP): persistent neuroadaptations in tetrapartite synapses that occur after chronic drug exposure.
Excitatory amino acid transporter 2 (EAAT2): a glutamate and aspartate transporter that is highly expressed in astroglia and is essential for rapid removal of glutamate from the synaptic cleft.
Extracellular matrix (ECM): a lattice-like support scaffold produced by neurons and glial cells that envelopes the soma, dendrites, and synapses, and functions in the mature brain to stabilize dendritic spine structure and regulate neurotransmission.
Gliotransmission: bidirectional communication between astrocytes and neurons through the release of chemical transmitters, including taurine, ATP, D-serine, and glutamate.
***In vivo* zymography:** a method to measure ECM remodeling using high-resolution imaging of the fluorescent degradation products of the introduced substrates.
Long-term depression (LTD): a persistent weakening in synaptic strength that can influence the storage of motor learning and memory.
Long-term potentiation (LTP): the persistent increase in the efficacy of synapses that is considered to be a crucial cellular mechanism for learning and memory.
Matrix metalloproteinases (MMPs): a large family of proteolytic zinc-containing endopeptidases that degrade specific ECM proteins. MMPs are either secreted into the extracellular milieu as proenzymes or are expressed in the plasma membrane.
Perineuronal nets (PNNs): ECM structures that surround the soma and proximal dendrites of some