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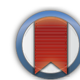

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RESEARCH HIGHLIGHT

Calcium-Impermeable NMDA Receptor: A Novel Target for Addiction

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Drug addiction results in long-term synaptic potentiation at excitatory synapses in the brain reward circuitry, especially in the ventral tegmental area (VTA) and nucleus accumbens (NAc), central parts of the mesolimbic dopamine system, and then progresses to other cortical regions [1, 2]. It has been proposed that a drug-induced increase in the AMPAR/NMDAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor/N-methyl-D-aspartate receptor) ratio in VTA dopamine (DA) neurons accounts for the synaptic potentiation by inserting Ca^{2+}-permeable AMPARs [3], and low-conductance Ca^{2+}-impermeable GluN3A-containing NMDARs in the same synapse [4]. Taken together, the enhanced excitatory synaptic transmission might contribute to altering DA neuron firing and therefore its release in target regions. However, it remained elusive whether the intrinsic excitability of DA neurons changes following acute cocaine exposure.

A recent study published in *The Journal of Neuroscience* by Creed *et al*. (2016) provides a further exploration of the excitability of VTA DA neurons following cocaine exposure, and points out unexpected roles of NMDAR remodeling in the process [5]. The authors report that the cocaine-evoked excitability of VTA DA neurons is largely modulated by hyperpolarization-activated cyclic nucleotide–gated channels and small-conductance Ca^{2+}-activated K^{+} (SK) channels [5]. It is known that blocking SK channels increases the burst firing of DA neurons. A previous study also demonstrated that SK channels and NMDARs form a Ca^{2+}-mediated feedback loop; blocking SK channels facilitates neuronal membrane hyperpolarization and decreases the afterhyperpolarization current (I_{AHP}) due to voltage-dependent Mg^{2+} blockade of the NMDARs. The authors found a dramatic decrease in the amplitude of the SK channel-mediated I_{AHP} in VTA DA neurons from cocaine-treated mice, indicating impairment of the SK channels. As a result, apamin (an SK2/3 channel blocker) fails to further enhance the firing in VTA DA neurons after cocaine exposure [5].

Considering the fact that cocaine induces the insertion of Ca^{2+}-impermeable NMDARs [4], this might disrupt the NMDAR-SK channel loop and contribute to the malfunction of SK channels after cocaine exposure. Creed *et al.* (2016) further tested this hypothesis on *GluN3A*-knockout mice, and confirmed the role of GluN3A-containing NMDARs in controlling the neuronal excitability after cocaine exposure. In addition, activating Group I metabotropic glutamate receptors (mGluRs) restores the GluR composition after cocaine exposure [4], and Creed *et al.* (2016) further reported the restoration of the firing increases and the I_{AHP} decrements in DA neurons.

Collectively, Creed *et al.* (2016) have demonstrated an unexpected role of non-canonical, Ca^{2+}-impermeable NMDARs in modifying neuronal excitability, by changing the functioning of Ca^{2+}-activated K^{+} channels. Nevertheless, it is worthwhile investigating whether the SK channel protein expression or activation mechanism changes after cocaine exposure. In addition, DA neurons display different firing patterns with different SK channel subunits; for instance, SK2 contributes to the firing precision but SK3 influences the firing frequency [6].

Multiple Ca^{2+} sources can activate SK channels, including voltage-gated Ca^{2+} channels, NMDARs,

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transient receptor potential channels, internal Ca^{2+} stores, and other receptors (such as mGluRs), and lead to increased Ca^{2+} signals. Previous studies have demonstrated that repeated amphetamine/ethanol exposure sensitizes the mGluR-induced potentiation of $I_{K(Ca)}$, consistent with Creed's study. This sensitization is correlated with changes in inositol 1,4,5-triphosphate signaling, and facilitates the burst-evoked Ca^{2+} signals in VTA DA neurons, as well as the induction of NMDAR-mediated long-term potentiation.

The Ca^{2+}-sensitivity of SK channels is determined by the calmodulin-binding domain. Casein kinase II (CK2) and protein phosphatase 2A (PP2A) modulate the Ca^{2+}-sensitivity of SK channels by phosphorylating or dephosphorylating SK-associated calmodulin. CK2 decreases the Ca^{2+}-sensitivity of the closed-state SK channel and PP2A increases the Ca^{2+}-sensitivity of the open-state SK channel. It has also been proposed that GluN3A-containing NMDARs negatively regulate the phosphorylation state of PP2A. Therefore, further studies are required to dissect the potential changes in Ca^{2+} dynamics and SK channel biophysics in DA neurons after drug exposure.

In this study, Creed *et al*. (2016) clarify the rationale that GluN3A-containing NMDARs are correlated with cocaine-evoked excitatory potentiation of VTA DA neurons. Actually, the endogenous GluN3A-containing NMDARs in brain have been implicated in various neuroprotective roles, especially reducing Ca^{2+} influx under conditions of Ca^{2+}-overload excitotoxicity, and are involved in the regulation of locomotion, cognition, olfaction, and pain perception [7], while GluN3A-containing NMDAR dysfunctions have been implicated in different diseases, such as Huntington's disease and mental disorders [7]. It is therefore highly plausible that similar changes in SK channel functioning could occur, and this would allow further therapeutic interventions.

The diheteromeric GluN3A-containing receptors are composed of GluN1 and GluN3A subunits forming glycine receptors, whereas the triheteromeric receptors concomitantly assemble GluN2 subunits to constitute NMDARs. Therefore the cocaine induced metaplasticity of NMDARs is mediated by triheteromeric NMDARs (such as GluN1/2A/3A or GluN1/2B/3A). Notably, the expression of GluN3A indicates synaptic immaturity or a dysfunctional state, for example depletion of GluN3A-containing NMDARs increases the NMDA currents and reduces the number of mushroom synapses in CA1 neurons [8], suggesting that cocaine-induced GluN3A insertion may cause mature synapses to regress to an immature state.

To sum up, NMDAR remodeling on DA neurons results in unexpected excitability changes, partly due to functional changes in K^{+} channels. Targeting Ca^{2+}-impermeable NMDARs might "switch" the neuron back to a physiological state and thus treat addiction. It will be interesting to find out whether pharmacological treatments or newly-developed invasive brain stimulation therapies, such as transcranial direct current stimulation or transcranial magnetic stimulation [9, 10], targeting these non-canonical NMDARs will be effective.

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