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Editorial Commentary

The meth brain: methamphetamines alter brain functions *via* NMDA receptors

Juliane Proft and Norbert Weiss

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Prague, Czech Republic

Commentary to: Functional changes in pyramidal neurons in the chronic methamphetamine-treated rat. (Gen. Physiol. Biophys. 2015, pp. 5–12)

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Methamphetamines (MAP) like crystal meth (MDA 3.4 methylendioxyamphetamine) and ecstasy (MDMA, 3.4 methylendioxymethamphetamine) are a group of neurotoxic drugs often used as a recreational drug and potentially to treat some neurological disorders. For instance, MDMA has been used as a therapeutic drug for posttraumatic stress disorder (PTSD) (Parrott 2014) as well as for attention deficit hyperactivity disorder (ADHD), although it has been declared as non-safe treatment due to its neurotoxicity and its addictive effect in human (Rusyniak 2013; Parrott 2014). Furthermore, addictive use of MAP derivatives has been shown to cause impaired learning and memory as well as other mental disorders (Schroder et al. 2003). In addition, an increased risk of Parkinson's disease (Bognar et al. 2013) has been documented in MPA users (Callaghan et al. 2012). Neurotoxicity of MPAs was explained by alteration of NMDA receptors and dopamine signaling pathways (Simoes et al. 2007; Ares-Santos et al. 2013). In addition, ecstasy binds to serotonin transporters and causes depletion of serotonin from its storage as well as release of dopamine and other neurotransmitters (White et al. 1996; Kish et al. 2010). Considerable efforts were made to characterize the influence of MAP derivatives on hippocampal structures in the brain, but little is known about the alterations in the sensory system, especially the piriform cortex, the area that is mostly known to sense odors (White et al. 1996).

In this issue of General Physiology and Biophysics, Hori et al. (pp. 5–12) treated rats chronically with MPA and investigated *via* electrophysiological recordings the influence of MPA on piriform cortex neurons, especially focusing on NMDA and AMPA receptors activity. The group observed the typical sniffing behavior and increase of movement in chronically-treated rats, the same behavior that is often observed in humans using MPA over a long period of time. These changes in behavior come with alterations of the morphology of dentrites of pyramidal cells. MPA-treated rats showed blebbing of the dentrites visible after staining with Lucifer yellow, to better identify the soma and dentrites of neurons. Blebbing of the cell typically occurs during apoptosis where the cytoskeleton breaks up causing an outward bulge of the cell membrane (Vermeulen et al. 2005). Blebbing can also play a role in other cellular processes like necrosis (Wyllie et al. 1980), chemical or physical stress, cell locomotion or division (Norman et al. 2010).

In addition, the authors observed a significant alteration of the electrical properties of the pyramidale neurons characterized by decrease of the membrane potential and input resistance of the cells. In order to further investigate the influence of MPA on neuronal network excitability and plasticity, transient post tetanic potentiation (PTP) and long-term potentiation (LTP) were analyzed (Gasparova et al. 2014). While PTP remains unaltered, LTP was significantly decreased in MPA-treated animals. In addition, ionotrophic application of AMPA and NMDA indicates an

Correspondence to: Juliane Proft, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10 Prague 6 – Dejvice, Czech Republic
E-mail: proft@uochb.cas.cz

Norbert Weiss, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Dejvice, Czech Republic
E-mail: weiss@uochb.cas.cz

altered AMPA/NMDA receptors activity in MPA-treated rats. Considering that NMDA and AMPA receptors represent the molecular substrate of LTP, it is likely that alteration of NMDA/AMPA response contributes to the alteration of LTP induced by MPA treatment.

Glutamatergic NMDA and AMPA receptors represent essential component of synaptic plasticity and long-term potentiation and depression (Luscher and Malenka 2012; Mokrushin and Pavlinova 2013). The observation that chronic treatment with MPA alters NMDA/AMPA response certainly represents an interesting molecular substrate for MPA-dependent alteration of cognitive functions. In addition, it is well accepted that alteration of NMDA and AMPA receptors significantly contribute to neurodegenerative disorders like Parkinson's and Alzheimer's diseases (You et al. 2012; Proft and Weiss 2014). Interestingly, a MPA-induced animal model for Parkinson's disease (Proft et al. 2011; Curtin et al. 2014; Tai et al. 2014) has been described. Moreover, a binding of MPA to α-synuclein has been reported and causes missfolding of α-synuclein, a key protein in Parkinson's disease (Tavassoly and Lee 2012). It is possible that missfolded α-synuclein could alter gluramatergic NMDA-dependent signaling pathway like it has been shown for missfolded amyloid (Proft and Weiss 2012; Stys et al. 2012; You et al. 2012).

Overall the results described in the paper by Hori et al. represent an interesting molecular substrate of how drug abuse might cause neurodegenerative disorders and a better understanding of the interaction of those drugs with key neuronal proteins will certainly highlight not only the molecular mechanism of drug-induced cognitive disorders but also potentially translate to a better basic understanding of those diseases.

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