ABSTRACT

ATTENUATION OF METHAMPHETAMINE AND NMDA-INDUCED TOXICITY BY LEPTIN IN MURINE STRIATUM

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Methamphetamine (METH) is a highly addictive illicit psychostimulant that is neurotoxic and causes permanent brain injury. METH-induced neurological damage affects areas of the brain that govern memory, emotions, motivation, cognition, critical thinking and association. In the striatum METH neurotoxicity intertwines several factors such as Dopamine (DA) overflow causing depletion, glutamate signaling, and free radicals formation causing oxidative stress. In addition, excessive dopaminergic innervation leads to severe reduction in DA terminals, which are measured by terminal markers tyrosine hydroxylase (TH) and DA transporters (DAT), and the decrease in activity and quantity of vesicular monoamine transporters (VMAT)-2. Brain imaging studies show METH use causes permanent damage which cannot be recovered even after three years of abstinence. METH-induced neurological damage colocalizes with degeneration that occurs in various neurodegenerative diseases such as Parkinson’s disease and Huntington’s disease. Therefore, understanding the mechanism of METH-induced neurodegeneration will provide an avenue towards identifying effective therapeutic targets for treatments of METH abuse and neurological disorders.

Several labs including ours have identified the neuroprotective capacity of endogenous peptides, such as somatostatin (SST) and neuropeptide Y (NPY), upon METH-induced toxicity in striatal neurons. Similarly, leptin is an important peripheral hormone produced mainly by adipose
tissue and is produced in proportion to fat stores, which circulates in the plasma, and is found ubiquitously in the central nervous system (CNS). Plasma leptin communicates energy stores in the periphery to the CNS. Most of the effects of leptin are attributed to the effects in the CNS. It can easily cross the blood brain barrier via its short-form receptor, ObRa. Though leptin is primarily known for its regulation of food intake and energy homeostasis governed by its receptors on hypothalamic neurons, it has been shown to serve other functions that deviate from its traditional role. Leptin mainly acts via its long form receptor ObRb that is found in hypothalamic and extra hypothalamic areas such as DA pathway, specifically in the ventral tegmental area (VTA), substantia nigra (SN), and nucleus accumbens (NAc), also in the striatum, cortex, cerebellum and hippocampus. The precise molecular pathway underlying the direct effects of leptin in these various regions is mostly unknown. But studies report that leptin administration decreases the firing rate of dopaminergic neurons causing decreased release in the VTA. The exact cellular mechanism for this reduced excitability by leptin remains to be determined. Using the above evidence as a backbone, along with preliminary data presented we have evidence that leptin signaling can be neuroprotective in striatal neurons upon METH-induced injury.

We know that METH-induced striatal injury is a multimodal function from DA overflow, glutamate signaling, free radicals formation and oxidative stress and published work from our lab and others provide some of the basis of the relationship between METH, DA, glutamate and oxidative stress. These identified pathways of how METH affects the striatum helped us to demonstrate the ways leptin can play a role. We hypothesized leptin will attenuate the METH-induced striatal neural injury. Our data suggests that leptin produced a dose dependent attenuation of apoptosis upon METH administration. When apoptotic death was compared to the total number of striatal neurons, METH caused about 25% of the striatal neurons to undergo apoptosis. However, leptin treatment protected apoptosis by 18% suggesting that leptin protects striatal
neurons from METH toxicity. We measured METH-induced hyperthermia is not prevented by leptin, one reason may be that it is an anorexogenic peptide and causes animals to increase activity and energy expenditure. In support of our hypothesis leptin treatment attenuates the ubiquitous over activation of the astrocytes and microglia caused by METH toxicity. Also, leptin attenuates oxidative stress, an effect of METH toxicity.

Furthermore, we demonstrate here that leptin mediates striatal neuroprotection by modulating glutamate transmission. We found that NMDA-mediated apoptosis is attenuated by leptin treatment. It also reduced the NMDA-induced formation of NO. However, leptin failed reduce striatal gliosis. A plethora of evidence demonstrates that METH induces neural damage in the striatum and other parts of the brain. Our contribution to this area of research is the finding that peripheral hormone, leptin, can protect degeneration caused by METH in the striatum.