

Amphetamine tolerance is caused by excess Ca^{++} influx through the NMDA receptor gated calcium channels on the outer membranes of the dopamine cells bodies in the ventral tegental area, one of two areas in the brain with concentrations of dopamine producing neurons.

As alluded to above, taking an appropriate NMDA* (partial) antagonist will prevent the development of a tolerance for the effects of an amphetamine or amphetamine-like stimulant. Also, by preventing excess Ca^{++} influx into the neuron, an NMDA antagonist will prevent associated brain alterations and damage (excitotoxicity).

Studies have indicated that amphetamine tolerance is prevented by exogenous or endogenous agents that are able to inhibit excess Ca^{++} influx into the neuron through the gated calcium channels on the neuronal membrane that have NMDA subtype glutamate receptors. Glutamate, the body's major excitatory neurotransmitter, opens the gated calcium ion channels upon attaching to the NMDA receptor. A number of other receptors are also expressed on these calcium channels, which, when stimulated, either facilitate or inhibit glutamate's action.

It is also important that agents that inhibit calcium channel activity not also cause deficient Ca^{++} influx. For example, ketamine is a full NMDA receptor antagonist, that prevents excess Ca^{++} influx and amphetamine tolerance. But being a full NMDA antagonist, ketamine in excessive doses results in deficient Ca^{++} influx. This could be one of the reasons it leaves K-user in a state of disassociation.

Magnesium is an NMDA antagonist. Most people are deficient in magnesium, and stress reduces magnesium levels. Whether or not one takes amphetamines, magnesium supplementation is very important for mood, general well-being and keeping stress levels under control. It is also important to take magnesium in efficient form, with adequate bioavailability. The best type is magnesium glycinate (chelated) with bioavailability at around 80%. Second best is magnesium carbonate with (I don't remember exactly) bioavailability at little above 30%. Supplemented magnesium should be at 500 mg/day level. Also there is a study which shows that children who use amphetamine-type stimulants have bad magnesium/calcium balance. Calcium levels stay the same with amphetamine usage, but magnesium levels drop.

* The NMDA receptor is a receptor for the neurotransmitter glutamate, which is the most important excitatory transmitter in the brain. It is not only a receptor, but also a channel (it is thus a ligand-gated ionic channel). N-methyl-D-aspartate is the famous agonist of the NMDA receptor, the latter being named after it. It is a very complex and fascinating ligand-gated channel that seems to be involved in the toxic effects of excessive glutamate, and in many other processes like synaptic plasticity and target recognition.