The selective protein kinase Cβ inhibitor, enzastaurin, decreases amphetamine stimulated locomotion and self-administration in rats
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Extracellular dopamine levels are regulated by the dopamine transporter (DAT), a transmembrane protein that takes up dopamine from the synapse into the cell. Amphetamines are substrates of DAT and reverse DAT function to release dopamine into the synapse. Amphetamines elicit their stimulating and reinforcing effects by increasing extracellular dopamine levels in the brain. Protein kinase Cβ (PKCβ) is important for amphetamine’s effects on outward transport without altering basic DAT function. Inhibition of PKCβ reduces amphetamine-stimulated dopamine efflux through the transporter in vitro and in vivo. The purpose of this study was to examine if PKCβ inhibition would decrease key amphetamine-stimulated behaviors: locomotion and self-administration. The selective PKCβ inhibitor, enzastaurin (1–30 pmol), was administered to male Sprague Dawley rats by intracerebroventricular injections 18 hours before behavioral evaluation. Locomotor activity was measured in infrared beam break boxes following administration of single doses (0.32–3.2 mg/kg) of amphetamine. In self-administration studies, rats earned infusions of amphetamine (0.032 mg/kg/infusion) or sucrose pellets under a fixed ratio 5 schedule of reinforcement for 60- or 20-minute sessions, respectively. Pretreatment with 10 pmol enzastaurin reduced locomotion following injections of 0.32 and 1 mg/kg amphetamine but the effect was surmountable at 3.2 mg/kg amphetamine, demonstrating a rightward shift in the amphetamine dose–effect curve. Enzastaurin (1 pmol) was not sufficient to decrease locomotor activity. Larger doses of enzastaurin (30 pmol) failed to further decrease amphetamine-stimulated locomotion. Enzastaurin decreased the number of amphetamine infusions earned by 60% but did not alter the number of sucrose pellets earned, suggesting that enzastaurin altered the reinforcing effects of amphetamine but not natural rewards. The data demonstrate that low doses of a specific PKCβ inhibitor attenuate amphetamine-mediated behaviors in a surmountable manner without non-selectively altering behavior. This study demonstrates that inhibition of PKCβ serves to reduce amphetamine reinforcement and could have therapeutic utility against amphetamine abuse.

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