

Behavioral sensitization to amphetamine results from an uncoupling between noradrenergic and serotonergic neurons.

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In rodents, drugs of abuse induce locomotor hyperactivity and repeating injections enhances this response. This effect, called behavioral sensitization, persists many months after the last administration, thus mimicking long-term sensitivity to drugs observed in human addicts. We show here that, in naïve animals, noradrenergic and serotonergic systems, besides their behavioral activating effects, inhibit each other via the stimulation of α_1 -adrenergic and 5-HT_{2A} receptors and that this mutual inhibition vanishes with repeated injections of d-amphetamine; this uncoupling may be responsible for behavioral sensitization. First, following repeated d-amphetamine injections, a d-amphetamine challenge induces a dramatic increase in cortical extracellular norepinephrine (NE) levels. This increased cortical NE release still occurs after one month withdrawal but is diminished or blocked if sensitization is performed in presence of prazosin, SR46349B, or a mixture of these α_1 -adrenergic and 5-HT_{2A} receptor antagonists, respectively. A strong correlation ($r^2=0.99$) between increases in cortical extracellular NE levels and the expression of behavioral sensitization was found. Second, repeated d-amphetamine injections induce an increased reactivity of serotonergic neurons measured by cortical extracellular serotonin (5-HT) levels following the administration of a 5-HT releaser, p-chloroamphetamine (PCA). PCA (7 mg/kg) was used because 2 mg/kg d-amphetamine did not modify cortical extracellular 5-HT levels. Third, mice knockout for α_1 -adrenergic (α_1 -AR KO) or 5-HT_{2A} (5-HT_{2A}-R KO) receptor respectively exhibit a behavioral and biochemical hyper-reactivity to the acute injection of PCA (α_1 -AR KO, 5-HT levels) and d-amphetamine (5-HT_{2A}-R KO, NE levels). Other results obtained in the laboratory indicate that these effects of d-amphetamine on NE and 5-HT neurons could be common to other drugs of abuse (Lanteri et al., this congress). In fact, uncoupling between noradrenergic and serotonergic neurons may occur not only in addiction but also during chronic stressful situations, thus facilitating the onset of mental illness.

Auclair et al., 2004, *Europ. J. Neurosci.*, 20: 3073-84.

Salomon et al., 2006, *PNAS (USA)*, 103: 7476-7481.