Drugs of abuse may be addictive because they disrupt a mutual regulation between noradrenergic and serotonergic neurons.

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Drugs of abuse, such as psychostimulants and opiates, induce in rodents a locomotor response. When drugs are repeatedly injected, animals develop a progressive increase of their locomotor response named behavioral sensitization. Studies on the neurobiological basis of behavioral sensitization of psychomotor-stimulant drugs have concentrated, despite inconstant results, on the midbrain dopamine (DA) systems and in particular on the mesoaccumbens DA neurons. However, the development and the expression of the behavioral sensitization to psychostimulants and opiates are completely inhibited by a pre-treatment with antagonists of alpha1b-adrenergic and 5-HT2A receptors, prazosin and SR46349B, respectively (1). More recently, we have found that four injections of d-amphetamine -one injection (2 mg/kg) every day- induced, after a 4-days or 1-month withdrawal, an increased release of norepinephrine (NE) or serotonin (5-HT) in mice prefrontal cortex in response to d-amphetamine or para-chloro-amphetamine (PCA, a 5-HT releaser), respectively (2). To test whether other drugs of abuse could trigger the same phenomenon, C57/Bl6 mice received every day during four days either cocaine (20 mg/kg), morphine (20 mg/kg) or ethanol (2g/kg) and same experiments as those done with d-amphetamine were performed after a 4-days withdrawal. All treatments induced increased releases of NE and 5-HT in mice prefrontal cortex. These increases did not appear when animals were pretreated with prazosin and SR46349B during sensitization. We propose that drugs of abuse share the common property to disrupt a mutual regulatory link between NE and 5-HT neurons. This dysregulation would make addicts hypersensitive to environment, a condition which may be the source of relapse.

(1) Auclair et al., 2004, Europ. J. Neurosci. 20: 3073-3084; (2) Salomon et al., 2006, PNAS (USA) 103: 7476-7481.