
The changes in dopamine system regulation occurring during stimulant administration are examined in relation to a new model of dopamine system function. This model is based on the presence of a tonic low level of extracellular dopamine that is released by the presynaptic action of corticostriatal afferents. In contrast, spike-dependent dopamine release results in a phasic, high concentration of dopamine in the synaptic cleft that is rapidly inactivated by reuptake. Tonic dopamine has the ability to down-modulate spike-dependent phasic dopamine release via stimulation of the very sensitive dopamine autoreceptors present on dopamine terminals. Stimulants are known to elicit locomotion and stimulate reward sites by releasing dopamine from terminals in the nucleus accumbens, which is followed by a rebound depression. It is proposed that the initial activating action of stimulants is caused by increasing the release of dopamine into the synaptic cleft to activate the phasic dopamine response. However, by interfering with dopamine uptake, stimulants also allow dopamine to escape the synaptic cleft, thereby depressing subsequent spike-dependent phasic dopamine release by increasing the tonic stimulation of the autoreceptor. In contrast, repeated stimulant administration is proposed to cause long-term sensitization by pharmacological disruption of a cascade of homeostatic compensatory processes. Upon drug withdrawal, the fast compensatory systems that were blocked by stimulants rapidly restore homeostasis to the system at a new steady-state level of interaction. As a consequence, the slowly changing but potentially more destabilizing compensatory responses are prevented from returning to their baseline conditions. This results in a permanent change in the responsivity of the system. Homeostatic systems are geared to compensate for unidimensional alterations in a system, and are capable of restoring function even after massive brain lesions or the continuous presence of stimulant drugs. However, the system did not evolve to deal effectively with repetitive introduction and withdrawal of drugs that disrupt dopamine system regulation. As a consequence, repeated insults to a biological system by application and withdrawal of drugs that interfere with its homeostatic regulation may be capable of inducing non-reversible changes in its response to exogenous and endogenous stimuli.


The effect of various drugs on the extracellular concentration of dopamine in two terminal dopaminergic areas, the nucleus accumbens septi (a limbic area) and the dorsal caudate nucleus (a subcortical motor area), was studied in freely moving rats by using brain dialysis. Drugs abused by humans (e.g., opiates, ethanol, nicotine, amphetamine, and cocaine) increased extracellular dopamine concentrations in both areas, but especially in the accumbens, and elicited hypermotility at low doses. On the other hand, drugs with aversive properties (e.g., agonists of kappa opioid receptors, U-50,488, tifluadom, and bremazocine) reduced dopamine release in the accumbens and in the caudate and elicited hypomotility. Haloperidol, a neuroleptic drug, increased...
extracellular dopamine concentrations, but this effect was not preferential for the accumbens and was associated with hypomotility and sedation. Drugs not abused by humans [e.g., imipramine (an antidepressant), atropine (an antimuscarinic drug), and diphenhydramine (an antihistamine)] failed to modify synaptic dopamine concentrations. These results provide biochemical evidence for the hypothesis that stimulation of dopamine transmission in the limbic system might be a fundamental property of drugs that are abused.


Behavioral sensitization caused by repeated and intermittent administration of psychostimulants, such as cocaine and D-amphetamine, is accompanied by enhanced function in limbic-motor circuitry that is involved in the generation of motivated behavior. The present microdialysis study investigated the effect of D-amphetamine-induced sensitization on dopamine (DA) efflux in the nucleus accumbens (NAC) of male rats during sexual behavior. Male rats were given one injection of D-amphetamine (1.5 mg/kg, i.p.) or saline every other day for a total of 10 injections. Three weeks after discontinuation of drug treatment, rats were tested for sexual behavior during a test in which microdialysis was performed. There was an augmented efflux of DA in the NAC of D-amphetamine-sensitized rats compared with nonsensitized control rats when a receptive female was present behind a screen (35 vs 17%). Sensitized rats exhibited facilitated sexual behavior when the screen was removed, as indicated by a significantly shorter latency to mount and an overall increase in the amount of copulatory behavior. Although there was a significant increase in NAC DA concentrations from baseline in both sensitized and nonsensitized rats during copulation, there was a greater increase in DA efflux in the NAC of sensitized rats during the first 10 min copulatory sample (60 vs 37%). These results demonstrate that behavioral sensitization caused by repeated psychostimulant administration can "cross-sensitize" to a natural behavior, such as sex, and that increased NAC DA release may contribute to the facilitation of appetitive and consummatory aspects of this behavior.


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