

## $\alpha_2$ -adrenoceptor number and function in rat brain after long-term administration of psychomotor stimulants

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Long-term administration of tricyclic antidepressant drugs to rats decreases the number of  $\alpha_2$ -adrenoceptors on neural membranes isolated from various areas of the brain and decreases the sensitivity to stimulation by clonidine of  $\alpha_2$ -adrenoceptors on noradrenergic neurons in hippocampal slices. Many antidepressant drugs are potent inhibitors of noradrenaline reuptake. One explanation for the changes in  $\alpha_2$ -adrenergic receptor function after long-term antidepressant drug administration is that sustained increases in synaptic neurotransmitter content causes down-regulation of presynaptic autoregulatory receptors. Certain psychomotor stimulants are thought to act by increasing synaptic noradrenaline and dopamine content by either directly releasing these neurotransmitters or by preventing their reuptake. In the present study the effects of four psychomotor stimulants, cocaine, d-amphetamine, methylphenidate and caffeine, were evaluated on the number and/or affinity of  $\alpha_2$ -adrenoceptors in various areas of the rat brain and upon the function of presynaptic  $\alpha_2$ -adrenoceptors in rat hippocampal slices.

Male Sprague-Dawley rats, 175-225 g, were injected twice daily, i.p., with saline or with cocaine, 3 mg/kg, d-amphetamine, 3 mg/kg, methylphenidate, 10 mg/kg, or caffeine, 50 mg/kg, for 14 days. The maximum number of binding sites ( $B_{max}$ ) and dissociation constants ( $K_D$ 's) were determined for the specific binding of  $^3H$ -clonidine to neural membranes isolated from six areas of the rat brain, the amygdala, brainstem, hypothalamus, hippocampus, parietal cortex and anterior caudate nucleus. In field stimulation studies, rat hippocampal slices were incubated with  $^3H$ -noradrenaline, 30 nM, for 15 min, washed with fresh buffer for 30 min and then stimulated (4 Hz, 2 msec duration, 2 min) at 12 min intervals. Cumulative concentration-effect curves were determined for the inhibition of  $^3H$ -noradrenaline release by clonidine, an  $\alpha_2$ -adrenergic receptor agonist. Complete frequency-response curves were also determined for fractional release of  $^3H$ -noradrenaline.

Long-term administration of cocaine, d-amphetamine and methylphenidate decreased the maximum number of specific binding sites for  $^3H$ -clonidine on neural membranes from the amygdala, brainstem, hypothalamus, and hippocampus. In contrast, treatment with caffeine for 14 days significantly increased specific binding of  $^3H$ -clonidine to membranes from the brainstem (68.2%) and hypothalamus (31.9%). No treatment altered the dissociation constants for  $^3H$ -clonidine binding to neural membranes from any brain area studied. Neither the frequency-response curves for field stimulation nor the clonidine concentration-effect curves determined on hippocampal slices were altered by long-term treatment with any of the four psychomotor stimulants. When added directly to the perfusate in a concentration of  $10^{-6}$  M, cocaine, d-amphetamine and methylphenidate, but not caffeine, shifted the frequency-response curves for field stimulation to the left.

The present study indicates that long-term administration of drugs which increase synaptic catecholamine content does not necessarily lead to a down-regulation of presynaptic  $\alpha_2$ -adrenoceptors. The changes in receptor density which were observed are presumably the result of changes in the density of postsynaptic  $\alpha_2$ -adrenoceptors.

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