

Rapid communication

ENDURING ENHANCEMENT IN AMPHETAMINE-STIMULATED STRIATAL DOPAMINE RELEASE IN VITRO PRODUCED BY PRIOR EXPOSURE TO AMPHETAMINE OR STRESS IN VIVO

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Animals given repeated intermittent injections of amphetamine (AMP) develop a hypersensitivity to the motor stimulant effects of AMP that persists for months following the cessation of drug treatment. This behavioral sensitization to AMP may be due to AMP's action as a stressor, because prior exposure to stress also produces an enduring hypersensitivity to the motor stimulant effects of AMP (Antelman and Chiodo, 1983). If this hypothesis is correct, sensitization to AMP and stress should be associated with similar long-lasting changes in the nervous system. We previously reported that the behavioral sensitization produced by AMP is accompanied by an enduring enhancement in AMP-stimulated endogenous dopamine (DA) release from striatal tissue in vitro (Robinson and Becker, 1982). The purpose of the present experiment was to determine if prior stress also produces an enduring enhancement in AMP-stimulated striatal DA release.

Ovariectomized (OVX) female rats were used for two reasons: (1) female rats show more robust sensitization than males; and (2) OVX eliminates the fluctuations in striatal DA release associated with the estrous cycle (Robinson and Becker, in press). Two weeks after OVX the rats received an i.p. injection of either 0.9% saline (SAL; 1 ml/kg) or 3.0 mg/kg d-AMP sulfate (3.0 mg/ml) once daily for 5 days. Because saline injections and the associated handling produce a typical 'stress response' (Sakellaris and Vernikos-Danellis, 1975) it was predicted that this alone would result in an

enduring enhancement in AMP-stimulated DA release, relative to non-handled control animals. Therefore, a third group of rats were left undisturbed during this time (non-handled controls; NH). Ten days after the last injection all rats were decapitated, the striatum dissected rapidly in ice-cold medium and then placed into superfusion chambers. Medium continuously flowed through the chambers at a rate of 100 μ l/min, and 5 min effluent samples were later assayed for DA. The superfusion method is described in detail by Becker et al. (1984). Following a 65 min equilibration period and collection of three baseline samples, 10 μ M d-AMP was added to the medium for 2.5 min, and an additional 5 samples collected.

The addition of AMP to the medium stimulated endogenous DA release from all chambers. However, as illustrated in fig. 1, there was a significant effect of pretreatment condition on AMP-stimulated striatal DA release ($F(5,4)$, $P = 0.011$). Striatal tissue obtained from AMP-pretreated rats released significantly more DA in response to AMP stimulation than tissue obtained from either SAL or NH rats. Furthermore, striatal tissue obtained from SAL rats released more DA than tissue obtained from NH rats (fig. 1). The three groups did not differ in basal levels of DA efflux prior to AMP stimulation, but it should be noted that basal DA efflux is not calcium- or temperature-dependent (Becker et al., 1984).

In summary, it was found that repeated intermittent exposure to AMP produces an enduring enhancement in AMP-stimulated DA release from striatal tissue in vitro, as previously reported

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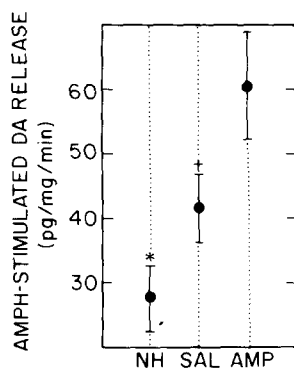


Fig. 1. Mean (\pm S.E.M.) amphetamine (AMP)-stimulated endogenous DA release from striatal tissue fragments (approximately 1 mm³) obtained from rats that 10 days previously received the last of 5 daily injections of saline (SAL; n = 11) or 3.0 mg/kg of AMP (n = 12), or were non-handled (NH; n = 5). The means represent the average release rate in pg DA/mg tissue per min over four 5 min intervals following the addition of 10 μ M AMP to the superfusion medium for 2.5 min. The average basal level of DA efflux was 13.4 ± 6.2 pg/mg per min. Statistical analyses were conducted on the log transformed data, and because the effects of SAL and AMP were predicted consisted of planned one-tailed t-tests. * NH differs from SAL (t = 1.76, P = 0.049), and AMP (t = 2.9, P = 0.005); † SAL differs from AMP (t = 1.86, P = 0.037).

(Robinson and Becker, 1982; Robinson and Becker, in press). More importantly, this is the first report that repeated intermittent exposure to the stress of saline injections (and associated handling) also produces an enduring (at least 10 days) enhancement in AMP-stimulated striatal DA release. Whether the greater effect of AMP over SAL pretreatment is due to some unique property of AMP, or because this is just a more potent stressor than SAL is not known. However, pre-

liminary data from this lab suggest that repeated immobilization stress is not more efficacious than SAL in enhancing DA release. Nevertheless, it is likely that an enduring enhancement in AMP-stimulated striatal DA release is at least partially responsible for the enduring hypersensitivity to the motor-stimulant effects of AMP seen in animals previously exposed to stress (Antelman and Chiodo, 1983). Furthermore, these data raise the possibility that enduring changes in brain DA systems produced by repeated exposure to stress contribute to the development of stress-precipitated psychopathology thought to involve brain DA dysfunction.

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