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BEHAVIORAL SENSITIZATION IS ACCOMPANIED BY AN ENHANCEMENT IN AMPHETAMINE-STIMULATED DOPAMINE RELEASE FROM STRIATAL TISSUE IN VITRO

TERRY E. ROBINSON * and JILL B. BECKER

Psychology Department and Neuroscience Laboratory Building, The University of Michigan, Ann Arbor, MI 48109, U.S.A.

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The repeated administration of amphetamine (AMPH) produces a long-lasting facilitation in the behavioral responsiveness to subsequent AMPH injections. This sensitization has been demonstrated using different behavioral indices (e.g. stereotypy, locomotion, rotational behavior), and in many different species (Kokkinidis and Anisman, 1980). Since sensitization in non-human animals is considered a model of AMPH psychosis in humans, knowledge of the neural changes underlying sensitization may provide an insight into the neural basis of AMPH psychosis (Kokkinidis and Anisman, 1980; Segal and Janowsky, 1978). Unfortunately, the neural substrate of sensitization has remained elusive (e.g., Conway and Uretsky, 1982). However, in a recent study we found that a single injection of AMPH produced a long-lasting (1 month) enhancement in AMPH-induced rotational behavior, and in AMPH-stimulated DA release from striatal tissue in vitro (Robinson et al., 1982). Therefore, we hypothesized that the behavioral sensitization produced by repeated AMPH injections would also be accompanied by an enhancement of striatal DA release.

Male Holtzman rats were injected i.p. with either 5 mg/kg of d-AMPH sulfate ($n = 18$) or saline ($n = 18$) twice daily for 5 consecutive days. Drug injections were then discontinued for 10 days. On the eleventh day after the last AMPH injection 10 of the AMPH and 10 of the saline pretreated rats were placed in wire hanging cages. After a 30 min habituation period they were injected with 3.0 mg/kg of AMPH and the occurrence of stereotyped behaviors was recorded every 5 min for 90 min, using the same stereotypy rating scale as Conway and Uretsky (1982). Conway and Uretsky (1982) showed this paradigm produces behavioral sensitization. We replicated their results. The AMPH-pretreated rats had a significantly higher cumulative stereotypy score (42.7 ± 2.8 S.E.M.) than did saline pretreated rats (22.3 ± 2.1; $U = 3$, $P < 0.001$).

The remaining animals, plus 6 additional naive rats were used for measuring endogenous DA release in vitro. After decapitation the striatum was dissected out and placed in a perifusion chamber positioned in a constant temperature bath (37°C). A medium (modified Krebs phosphate buffer) flowed through the chamber at a rate of 100 μl/min. After a 45 min equilibration period samples of the effluent were collected at 5 min intervals, and these effluent samples assayed for DA. See Becker and Ramirez (1981) and Robinson et al. (1982) for a detailed description of the techniques. Normal medium was infused through the chamber for the first 20 min (intervals 1–4). During intervals 5–6, 10^{-6} M d-AMPH was added to the medium, followed by normal medium for intervals 7–10. During intervals 11–12 60 mM KCl was added to the medium, with the concentration of NaCl reduced to prevent changes in osmotic pressure. Normal medium was restored for intervals 13–14.

The level of basal (intervals 1–4), AMPH-stimulated (intervals 5–8) and K^+-stimulated (intervals 11–13) DA release was nearly identical in saline-pretreated and naive rats. Therefore, data from these animals were pooled (control group,

* To whom all correspondence should be addressed: Neuroscience Building, 1103 E. Huron St., Ann Arbor, MI 48109, U.S.A.

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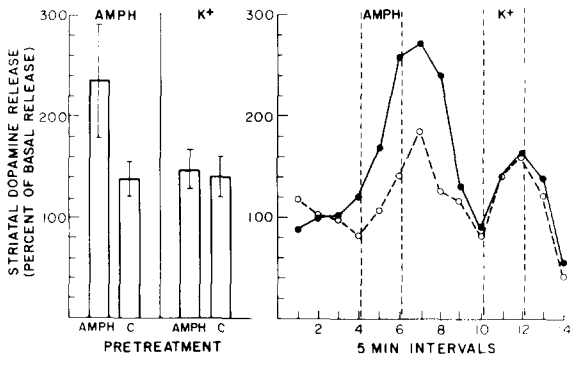

Fig. 1. AMPH and K^+-stimulated endogenous DA release from striatal tissue in vitro. DA release is expressed as a percent of basal release (average DA release over intervals 1–4; see time course to right). *Left*: The bars represent the average (±S.E.M.) level of AMPH (intervals 5–8) and K^+ (intervals 11–13)-stimulated DA release from AMPH-pretreated (AMPH) and control (C) rats. AMPH-stimulated DA release from AMPH-pretreated rats is significantly greater than from control rats ($P < 0.02$). AMPH-pretreated and control animals do not differ in the level of K^+-stimulated DA release. *Right*: Time course of DA release for each 5 min interval. AMPH or K^+ was added to the infusion medium where indicated by the vertical dashed lines. Closed circles = AMPH-pretreated; open circles = control (see text).

n = 14). There was no difference in basal DA release between AMPH pretreated and control animals (29.3 ± 3.4 vs. 36.3 ± 3.3 pg DA/mg tissue per min, respectively). The addition of AMPH to the medium produced an increase in DA release in all cases. However, the increase was significantly greater in striatal tissue obtained from AMPH pretreated animals (average increase of 235 ± 56% S.E.M., over basal release) than from control animals (138 ± 17%; fig. 1; $t = 2.2$, $P < 0.02$). Interestingly, there was no difference between the groups in K^+-stimulated DA release (fig. 1).

In summary, the behavioral sensitization produced by repeated AMPH injections is accompanied by an increase in the responsiveness of striatal tissue to AMPH. Of course, a more complete study relating the time course of behavioral sensitization with the enhancement in AMPH-stimulated DA release is required to convincingly argue that the change in striatal DA release mediates sensitization. Nevertheless we suggest that further studies on the neural basis of sensitization may be more profitable if focussed on presynaptic, rather than postsynaptic mechanisms. Furthermore, differences between AMPH-stimulated and K^+-stimulated DA release may provide clues as to the nature of the change in the release process produced by the repeated administration of AMPH.

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