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Mifepristone prevents the expression of long-term behavioural sensitization to amphetamine

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Abstract

Three weeks following intermittent amphetamine exposure (2.5 mg/kg/day for 5 days), rats showed an enhanced locomotor response to an amphetamine challenge. Mifepristone (20 mg/kg) given 45 min prior to the challenge completely prevented the expression of amphetamine hyperresponsiveness. The glucocorticoid antagonist did not affect the locomotor response to amphetamine in drug-naive rats. These data demonstrate for the first time that glucocorticoid receptor antagonist treatment may prevent long-term hyperreactivity to drugs of abuse in individuals with a drug history.

Keywords: Amphetamine; Behavioral sensitization; Glucocorticoid

Single or repeated exposure to psychomotor stimulants and stress produces an enduring enhancement of the locomotor stimulating and reinforcing effects of drugs of abuse. This phenomenon, called behavioural sensitization, is currently being evaluated as a potential model for drug addiction and drug-induced and idiopathic psychoses (for reviews: Kalivas and Stewart, 1991; Robinson and Becker, 1986; Robinson and Berridge, 1993). Regarding the mechanisms involved, a role of the hypothalamus-pituitary-adrenal (HPA) axis in behavioural sensitization, as one of the pathways common to repeated stimulus exposure, is now under intensive investigation. Thus far, several studies have suggested a critical role for the HPA axis, i.e. glucocorticoids, in the initiation of drug- and stress-induced behavioural sensitization (Cole et al., 1990; Deroche et al., 1992). However, a possible involvement of glucocorticoids in the enduring nature and expression of behavioural hyperresponsiveness has received less attention. Very few studies have explored the possibility of using glucocorticoid receptor antagonists as pharmacological tools to interfere with the sensitization process. The present study was designed to address this issue. More specifically, we tested whether blockade of glucocorticoid receptors by Mifepristone (RU486) modulated the expression of behavioural sensitization long (3 weeks) after animals were sensitized to amphetamine. The results showed, for the first time, that a glucocorticoid receptor antagonist may abolish hyperreactivity to drugs of abuse in individuals with a drug history.

Male Wistar rats (Harlan, Zeist, Netherlands), maintained on a normal light/dark cycle, weighing 160–180 g at the beginning of the experiment were divided into two groups of 16 animals. One group received amphetamine (2.5 mg/kg, i.p.) once daily for 5 consecutive days. The other group received saline. Three weeks following the last injection, the rats were allowed to adapt to locomotor cages (40 × 40 × 30 cm) for 120 min. Subsequently, half of the amphetamine- and the saline-pretreated animals received Mifepristone (kindly donated by Organon, Oss, Netherlands) at a dose of 20 mg/kg, s.c. suspended in a 5% mulgofen/saline solution. The remaining rats received vehicle. Locomotor activity was then monitored for 45 min using a video-tracking system (EthoVision, Noldus Information Technology, Wageningen, Netherlands). Subsequently, all animals received an i.p. injection of 1.0 mg/kg amphetamine and locomotor activity was recorded for 120 min. The position of the animal was read five times/s and locomotor activity was calculated and expressed as dis-

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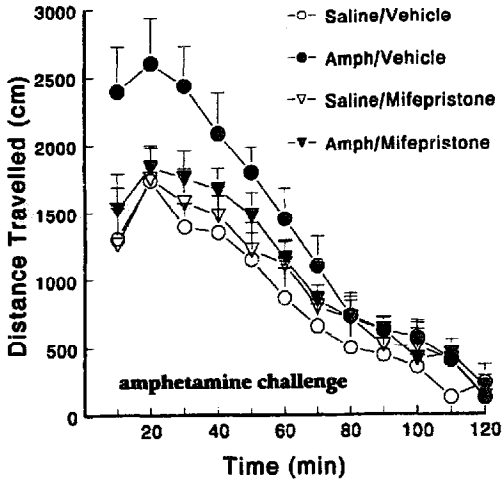

Fig. 1. Locomotor response to amphetamine (1.0 mg/kg, i.p.) in saline- and amphetamine-pretreated rats (2.5 mg/kg/day, i.p., for 5 days) following a 3-week interval. Half the animals received Mifepristone (20 mg/kg, s.c.) 45 min prior to amphetamine challenge, the other half its vehicle. Note that Mifepristone prevented the enhanced locomotor response to amphetamine in amphetamine-pretreated rats, but did not affect the acute locomotor response to amphetamine in saline-pretreated rats. Data are expressed as mean distance travelled (cm) ± S.E.M. per 10-min interval ($n = 8$ per group).

tance travelled (cm) per 10-min interval.

As shown in Fig. 1, saline-pretreated rats injected with vehicle on the test day showed a characteristic locomotor response to amphetamine. The response to amphetamine was markedly enhanced in animals pretreated with the psychostimulant, indicating that sensitization to the locomotor stimulating effects of amphetamine had occurred (group versus time, $F(2,93)$, $P = 0.002$, two-factor repeated measures analysis of variance). Mifepristone, given 45 min prior to amphetamine challenge, did not affect the acute locomotor response to amphetamine in saline-pretreated animals ($F(0,28)$, n.s.), but prevented the enhanced locomotor response to amphetamine in amphetamine-pretreated rats ($F(2,17)$, $P = 0.019$, compared to amphetamine-pretreated rats injected with vehicle). Habituation scores and locomotor activity in response to Mifepristone or vehicle were not significantly different among groups (data not shown).

The present study clearly showed that administration of the glucocorticoid receptor antagonist, Mifepristone, completely prevented the expression of amphetamine-induced behavioural sensitization, with no effect on the acute locomotor stimulating effect of amphetamine. These data suggest that activation of glucocorticoid receptors plays a crucial role in the manifestation of long-term behavioural sensitization. The effect of the glucocorticoid antagonist may depend on changes in the activity of dopaminergic neurons projecting to the striatal complex. The plausibility of this suggestion is supported by the fact that (1) the expression of sensitization is believed to involve enhanced striatal dopamine (DA) transmission (for review, see Kalivas and Stewart, 1991) and (2) glucocorticoid receptors are present on mesencephalic DA neurons (Härfstrand et al., 1986). Furthermore, corticosterone has been shown to potentiate the locomotor response to amphetamine (Mormède et al., 1994). Interestingly, we recently found that repeated exposure to cocaine resulted in a long-lasting enhancement of corticosterone secretion induced by the psychostimulant (Schmidt et al., 1995). Therefore, hypersecretion of corticosterone as a result of repeated psychostimulant administration may contribute to the enhanced (DA-dependent) behavioural responses elicited by these drugs.

Further pharmacological analysis of the effect of Mifepristone just described, as well as its effect on drug self-administration, is in progress. These studies may lead to the development of intervention strategies for readjusting neuronal functioning in drug addicts.

References

Cole, B.J., M. Cador, L. Stinus, C. Rivier, J. Rivier, W. Vale, M. Le Moal and G.F. Koob, 1990, Critical role of the hypothalamic pituitary adrenal axis in amphetamine-induced sensitization of behavior, Life Sci. 47, 1715.

Deroche, V., P.V. Piazza, P. Casolini, S. Maccari, M. Le Moal and H. Simon, 1992, Stress-induced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion, Brain Res. 598, 343.

Härfstrand, A., K. Fuxe, A. Cintra, L.F. Agnati, I. Zini, A.C. Wilkström, S. Okret, Z.Y. Yu, M. Goldstein, H. Steinbusch, A. Verhofstad and J.A. Gustafsson, 1986, Glucocorticoid receptor immunoreactivity in monoaminergic neurons of rat brain, Proc. Natl. Acad. Sci. USA 238, 302.

Kalivas, P.W. and J. Stewart, 1991, Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity, Brain Res. Rev. 16, 223.

Mormède, P., J. Dulluc and M. Cador, 1994, Modulation of the locomotor response to amphetamine by corticosterone, Ann. N.Y. Acad. Sci. 746, 394.

Robinson, T.E. and J.B. Becker, 1986, Enduring changes in brain and behaviour produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis, Brain Res. Rev. 11, 157.

Robinson, T.E. and K.C. Berridge, 1993, The neural basis of drug craving: an incentive-sensitization theory of addiction, Brain Res. Rev. 18, 247.

Schmidt, E.D., F.J.H. Tilders, A.W.J.W. Janszen, R. Binnekade, T.J. De Vries and A.N.M. Schoffelmeer, 1995, Intermittent cocaine exposure causes delayed and long-lasting sensitization of cocaine-induced ACTH secretion in rats, Eur. J. Pharmacol. 285, 317.