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Short communication

Effects of acute D-CPPene on mesoaccumbens dopamine responses to nicotine in the rat

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Abstract

Acute administration of the NMDA receptor antagonist, D-CPPene (SDZ EAA 494; 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid; 2 mg/kg), abolished ($P < 0.01$) the sensitised mesoaccumbens dopamine response to nicotine (0.4 mg/kg) measured using in vivo microdialysis, but not the increased locomotor activity, observed in rats pretreated with nicotine prior to the test day. D-CPPene enhanced ($P < 0.01$) the mesoaccumbens dopamine response, but not the locomotor response, to acute nicotine given to drug-naive rats. The data suggest that sensitised mesoaccumbens dopamine responses to nicotine involve co-stimulation of NMDA receptors but that this effect is not closely related to sensitisation of the locomotor response to the drug.

Keywords: Nicotine; D-CPPene (SDZ EAA 494; 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid); Sensitization; Dopamine, mesoaccumbens; Locomotor activity

1. Introduction

Nicotine is a psychostimulant drug of dependence which shares many of the psychopharmacological properties of cocaine and amphetamine (Balfour, 1990). In addition, like many other drugs of dependence, it preferentially increases the release and turnover of dopamine in the nucleus accumbens (Clarke et al., 1988; Di Chiara and Imperato, 1988), a response which has been implicated in both the locomotor stimulant properties of the drug (Clarke et al., 1988; Imperato et al., 1986; Balfour, 1990) and its ability to reinforce self-administration (Corrigall et al., 1992, 1994). In common with other psychostimulant drugs of abuse, intermittent pretreatment with nicotine results in sensitisation of the mesoaccumbens dopamine response to the drug (Benwell and Balfour, 1992) and this sensitisation is attenuated or abolished if NMDA receptor antagonists are co-administered during the pretreatment phase of the experiment (Shoaib et al., 1994). The antagonists, however, do not appear to attenuate the sensitised locomotor responses observed in nicotine-pretreated rats (Shoaib et al., 1994). This is a surprising finding since the evidence that the stimulation of locomotor activity evoked by nicotine depends upon stimulation of the mesoaccumbens system seems robust (Clarke, 1990; Balfour, 1990). In the present study the competitive NMDA antagonist D-CPPene (SDZ EAA 494; 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid) has been used to explore further the relationship between dopamine overflow in the nucleus accumbens and the locomotor responses to nicotine in the rat.

2. Methods and materials

2.1. Animals

The experiments were performed with male Sprague-Dawley rats bred in the Biomedical Services Unit at Ninewells Hospital and Medical School from stock purchased from Interfauna, Huntington, Cambridgeshire, UK. The animals weighed approximately 250 g at the beginning of the experiment. They were housed in pairs during the pretreatment phase and singly following surgery. They were allowed free access to food and water. The holding room lights were on between 06:00 h and 18:00 h daily.

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2.2. Treatment protocol

In all experiments, prior to surgery, the animals were pretreated with 5 daily subcutaneous (s.c.) injections of nicotine (0.4 mg/kg) in order to sensitise them to the drug (Benwell and Balfour, 1992). Control animals were given saline (1 ml/kg; controls). At least 3 h after the last s.c. injection on day 5, dialysis probes were located in the nucleus accumbens under halothane anaesthesia using the procedure and coordinates described by Benwell and Balfour (1992). Using these coordinates (1.7 mm rostral and 1.5 mm lateral to bregma and 7.5 mm vertically from the surface of the brain according to Paxinos and Watson (1986)), the probe was located predominantly in the core of the structure. Eighteen hours later, the animals were transferred to activity boxes and the dialysis probes were connected to a syringe pump which delivered a Ringer solution, composed of NaCl (147 mM), KCl (4 mM) and $CaCl_2$ (1.25 mM) at a constant rate of 1.7 μl/min. The animals were left for at least 60 min to allow the system to equilibrate before 3 × 20 min dialysis samples were collected and analysed for dopamine and dihydroxyphenylacetic acid using high pressure liquid chromatography with electrochemical detection (Benwell and Balfour, 1992). The animals were then given intraperitoneal injections of D-CPPene (2 mg/kg) or saline (2 ml/kg) 40 min before the injection of nicotine (0.4 mg/kg). Locomotor activity was measured using photobeams arrayed along the sides of the activity box (Benwell and Balfour, 1992). In each experiment the mean levels of dopamine and dihydroxyphenylacetic acid in the baseline dialysate samples were calculated and the overflow was expressed as a percentage of this mean. The responses to the treatments were evaluated statistically using analysis of variance for repeated measures. All the experiments were performed in full accordance with UK Home Office regulations and were covered by Home Office Project License number PPL 60/01115.

2.3. Drugs

Nicotine hydrogen tartrate, purchased from Sigma, was dissolved in saline and the pH corrected to 7.0 by the addition of a small quantity of NaOH. The dose is expressed as the free base. D-CPPene (SDZ EAA 494) was a generous gift from Sandoz (Basel, Switzerland) and was dissolved in saline and injected in a volume of 2 ml per kg.

3. Results

The basal levels of dopamine in the dialysates measured prior to the first injection on the test day were 0.086 ± 0.014 and 0.110 ± 0.021 pmol/20 μl for the rats pretreated with saline and nicotine respectively; the basal

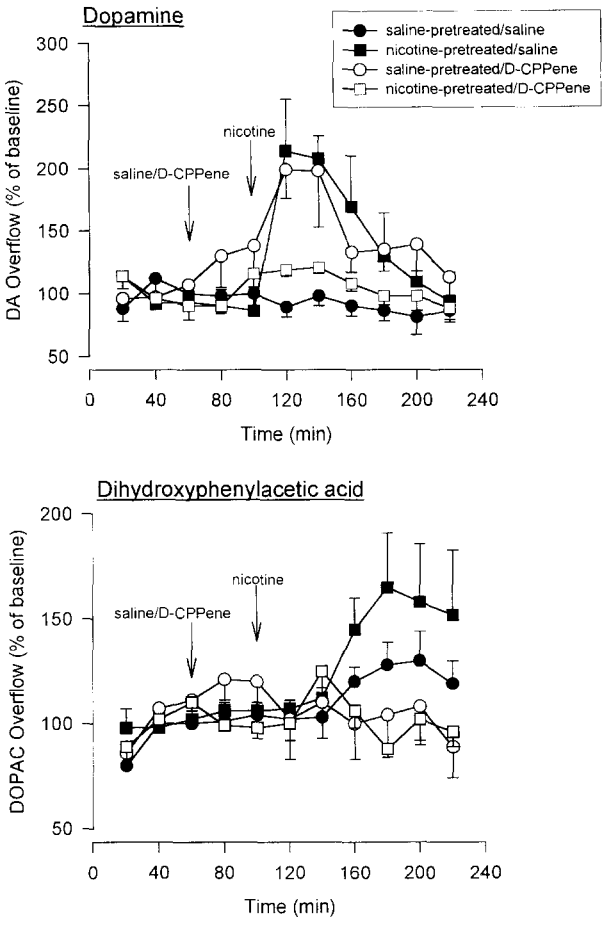

Fig. 1. The effects of D-CPPene on the increase in dopamine and dihydroxyphenylacetic acid overflow in the nucleus accumbens evoked by nicotine. Groups of rats were pretreated for 5 days with daily s.c. injections saline (circles) or nicotine (0.4 mg/kg; squares). Dopamine and dihydroxyphenylacetic acid overflow were measured on day 6. D-CPPene (2 mg/kg i.p.) or saline (2 ml/kg i.p.) was injected at the point indicated by the first arrow; nicotine (0.4 mg/kg s.c.) was injected at the point indicated by the second arrow. The data are expressed as means ± S.E.M. of 5 observations.

levels of dihydroxyphenylacetic acid in the dialysates were 25.5 ± 4.1 and 17.4 ± 3.5 pmol/20 μl for the rats pretreated with saline and nicotine respectively. In neither case were the differences between values for the saline- and nicotine-pretreated rats statistically significant. Dopamine overflow in the nucleus accumbens was increased significantly by the injection of nicotine ($F(10,150) = 6.4$; $P < 0.001$) but not by the intraperitoneal injection of saline or D-CPPene (Fig. 1). The analysis also revealed that this response was influenced both by the pretreatment the animals received prior to the test day and the injection of D-CPPene on the test day prior to the challenge dose of nicotine (pretreatment × D-CPPene × time $F(10,150) = 4.5$; $P < 0.001$). Subsequent analysis showed that dopamine overflow was increased ($P < 0.01$) in nicotine-pretreated animals (nicotine-sensitised rats) given an intraperitoneal injection of saline prior to the nicotine injection on the test day whereas in saline-pre-

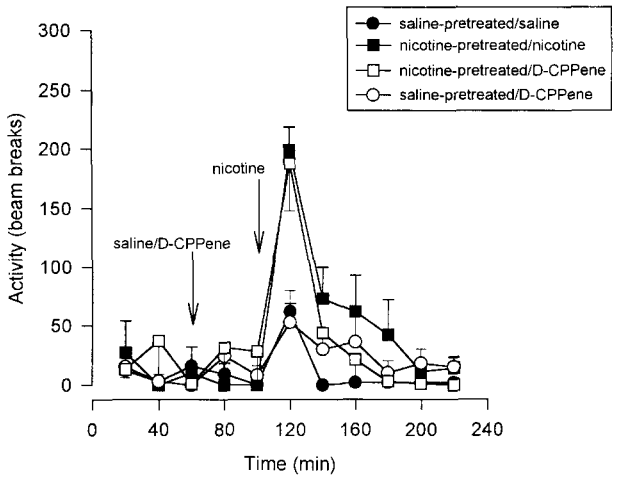

Fig. 2. The effects of D-CPPene on the increase in locomotor activity evoked by nicotine. Groups of rats were pretreated for 5 days with daily s.c. injections saline (circles) or nicotine (0.4 mg/kg; squares). Locomotor responses were measured on day 6. D-CPPene (2 mg/kg i.p.) or saline (2 ml/kg i.p.) was injected at the point indicated by the first arrow; nicotine (0.4 mg/kg s.c.) was injected at the point indicated by the second arrow. The data are expressed as means ± S.E.M. of 5 observations.

treated rats, nicotine increased ($P < 0.05$) dopamine overflow in the rats given intraperitoneal D-CPPene but not intraperitoneal saline. In rats given intraperitoneal saline, nicotine also increased the overflow of dihydroxyphenylacetic acid (Fig. 1). This response to nicotine was not influenced significantly by pretreatment with the drug prior to the test day but was abolished by the prior administration of D-CPPene on the test day (D-CPPene × time $F(10,150) = 3.8$; $P < 0.01$).

In agreement with previous studies, nicotine pretreatment prior to the test day enhanced the locomotor stimulant response to the drug (pretreatment × time $F(10,150) = 8.4$; $P < 0.001$; Fig. 2). This response was unaffected by the administration of D-CPPene prior to the nicotine injection. In addition, D-CPPene did not influence the locomotor response to acute nicotine.

4. Discussion

The principal finding in the present study is that the acute administration of D-CPPene to rats pretreated with nicotine suppresses the sensitised mesoaccumbens dopamine response to the drug seen in these rats while having no effect on the enhanced locomotor stimulation also seen in these animals. In contrast, the administration of D-CPPene to saline-pretreated rats enhanced the mesoaccumbens dopamine response to a nicotine injection but had no effect on locomotor response to nicotine. Thus, these data provide further evidence for a dissociation between increased dopamine overflow in the core of the nucleus accumbens and the locomotor stimulant properties of nicotine. They do not, however, preclude a role for mesoaccumbens dopamine in the expression of sensitised locomotor responses to nicotine since these may be mediated post-synaptically. The results also indicate that the mechanisms underlying the interaction between nicotine and D-CPPene are complex and are influenced by pretreatment with nicotine prior to the test day. The data imply that the expression of sensitised mesoaccumbens dopamine responses seen in nicotine-pretreated rats depends upon co-stimulation of NMDA receptors. This conclusion is consistent with results reported recently by McGehee et al. (1995) which showed that nicotine can stimulate glutamate secretion in the brain by acting on receptors located presynaptically on glutamate-secreting terminals. If this is the case the enhanced dopamine responses seen in saline-pretreated rats challenged acutely with nicotine following an injection of D-CPPene are difficult to explain since they suggest that stimulation of NMDA receptors attenuates the effects of acute nicotine on dopamine overflow in the nucleus accumbens. In contrast to its effects on dopamine overflow evoked by nicotine, D-CPPene consistently attenuated the increase in dihydroxyphenylacetic acid overflow evoked by an injection of nicotine in both drug-naive and nicotine-sensitised rats. These data suggest that the mechanisms by which nicotine pretreatment and D-CPPene enhance the dopamine responses to nicotine may be different. Nicotine exerts its effects in the brain by interacting with a family of neuronal nicotinic receptors with different anatomical locations (Wonnacott, 1990). It is possible, therefore, that the receptors which enhance dihydroxyphenylacetic acid overflow and which mediate the dopamine responses to subchronic nicotine are a different isoform or have a different location to those which mediate the responses to acute nicotine which are enhanced by D-CPPene.

The study has also shown that acute blockade of NMDA receptors on the test day has the same effects on dopamine overflow in the nucleus accumbens and locomotor activity as those reported previously for rats given the antagonist during the pretreatment phase but not on the test day (Shoaib et al., 1994). These results imply that expression of sensitised mesoaccumbens dopamine responses to nicotine may depend upon the co-stimulation of NMDA receptors both during the pretreatment phase of the experiment and on the test day although they do not exclude the possibility that the attenuation of the sensitised responses in animals given the drug during the pretreatment phase may be related to a prolonged blockade of the NMDA receptors which persists for many hours after administration of the antagonist.

Acknowledgements

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References

Balfour, D.J.K., 1990, Nicotine as the basis of the tobacco smoking habit, in: Psychotropic Drugs of Abuse – Section 130 of the International Encyclopedia of Pharmacology and Therapeutics, ed. D.J.K. Balfour (Pergamon Press, New York, NY) p. 453.

Benwell, M.E.M. and D.J.K. Balfour, 1992, The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity, Br. J. Pharmacol. 105, 849.

Clarke, P.B.S., 1990, Dopaminergic mechanisms in the locomotor stimulant effects of nicotine, Biochem. Pharmacol. 40, 1427.

Clarke, P.B.S., D.S. Fu, A. Jakubovic., and H.C. Fibiger, 1988, Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats, J. Pharmacol. Exp. Ther. 246, 701.

Corrigall, W.A., K.B.J. Franklin, K.M. Coen and P.B.S. Clarke, 1992, The mesolimbic dopamine system is implicated in the reinforcing effects of nicotine, Psychopharmacology 107, 285.

Corrigall, W.A., K.M. Coen and K.L. Adamson, 1994, Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area, Brain Res. 653, 278.

Di Chiara, G. and A. Imperato, 1988, Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats, Proc. Natl. Acad. Sci. USA 85, 5274.

Imperato, A., A. Mulas and G. Di Chiara, 1986, Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats, Eur. J. Pharmacol. 132, 337.

McGehee, D.S, M.J.S. Heath, S. Gelber, P. Devay and L.W. Role, (1995) Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors, Science 269, 1692.

Paxinos, G. and C. Watson, 1986, The Rat Brain in Stereotaxic Coordinates, 2nd edn. (Academic Press, New York, York).

Shoaib, M., M.E.M. Benwell, M.T. Akbar, I.P. Stolerman and D.J.K. Balfour 1994, Behavioural and neurochemical adaptations to nicotine in rats: influence of NMDA antagonists, Br. J. Pharmacol. 111, 1073.

Wonnacott, S., 1990, Characterization of brain nicotine receptor sites, in: Nicotine Psychopharmacology: Molecular, Cellular and Behavioural Aspects, eds. S. Wonnacott, M.A.H. Russell and I.P. Stolerman (Oxford University Press, Oxford) p. 226.