Effects of Methamphetamine on Dopamine Cells in the Substantia Nigra Pars Compacta and the Ventral Tegmental Area

Katsuo KAMATA and Tsutomu KAMEYAMA
Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan
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Abstract—The ability of methamphetamine to inhibit the firing rate of dopamine cells in the substantia nigra pars compacta (SNC) and the ventral tegmental area (VTA) was studied. Methamphetamine reduced the firing rates of the dopamine cells in a dose-dependent manner in the SNC and the VTA. The doses of methamphetamine required to produce a 50% inhibition of firing rate in the SNC and the VTA were 0.37 mg/kg and 0.28 mg/kg, respectively.

Amphetamine or methamphetamine-induced increased locomotor activity and stereotyped behaviour is a widely accepted animal model of paranoid schizophrenia (1-5). An accumulating body of evidence suggests that amphetamine or methamphetamine increases the release and blocks the reuptake of newly synthesized dopamine at the nerve terminal (6-9). Low doses of amphetamine and methamphetamine induce increased locomotor activity, and high doses cause focused stereotypy. Although the mode of action of methamphetamine is well-known and has been investigated by a variety of approaches, surprisingly, there has been no electrophysiological investigation of this drug. Thus, the aim of this study was to examine the effects of acute doses of methamphetamine on dopamine cells in the SNC and the VTA.

All experiments were carried out on male Wistar rats weighing 250-350 g. The surgical procedure for single unit recording has been described previously (10, 11). Briefly, 26 rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and mounted in a stereotaxic apparatus. Anesthesia was maintained by supplementary i.p. injection as required. The body temperature was maintained at 37±0.5°C. A midline incision was made, and the skin and muscle of the head were reflected to expose the cranium. A 3 mm burr hole was drilled through the skull overlying the SNC (2.8-3.0 mm anterior to lambda, 1.8-2.0 mm lateral to the midline, 6.5-8.0 mm from the surface) and the VTA (2.8-3.0 mm anterior to lambda, 0.5-0.8 mm lateral to the midline, 6.5-8.0 mm from the surface) according to the atlas of König and Klippel (12). The area surrounding the wound was sprayed with 8% xylocaine after the skull was exposed. A glass microelectrode filled with 2.0 M NaCl with 2% pontamine sky blue and having an impedance of 4-8 MΩ at 1 KHz was lowered through the burr hole. Single unit discharges were passed through a high-impedance amplifier, monitored on an oscilloscope and recorded with a rate-meter. Methamphetamine HCl was dissolved in saline and was injected via a femoral vein catheter. When drugs were injected, the doses were calculated as the free base. Only one cell was studied in each animal. A 5 min period of baseline activity was recorded before the first i.v. injection of methamphetamine. Increasing doses of methamphetamine were then administered, at 2 min intervals, so that the cumulative dose after each injection was twice the cumulative dose before the injection (i.e., individual doses of 0.25, 0.25, 0.5 and 1.0 mg/kg result in a final cumulative dose of 2.0 mg/kg). The percent change in firing after each dose was determined by comparing the response, averaged over successive 10 sec intervals during the 2 min period after each injection,
with the average baseline rate before drug. At the end of each experiment, the location of the tip of the electrode was marked by ejection of pontamine sky blue and confirmed by microscopic examination.

The activity pattern of all dopamine neurones in the SNC and the VTA met the criteria for spontaneously active dopamine neurones (10, 11, 13-15). In fact, many of these neurones were typically firing at rates of 3.1±0.2 spikes/sec, have multiphasic (+/−/+ ) action potential and duration of 2.5–4.5 msec, have an initial segment-somatodendritic (IS-SD) break in the early rising phase, and frequently display a train of decreasing amplitude action potentials (i.e., burst) upon discharge. The effects of increasing incremental doses of methamphetamine on the activity of dopamine neurones in the SNC and the VTA are shown in Fig. 1. As can be seen in Figs. 1 and 2, methamphetamine inhibited the dopamine cells in a dose-dependent manner both in the SNC and the VTA. A subsequent injection of haloperidol reversed the response in both cases. The doses of methamphetamine required to produce a 50% inhibition of activity in the SNC and the VTA were 0.37 ±0.04 mg/kg (mean±S.E., n=12) and

0.28±0.03 mg/kg (n=14), respectively.

The present results show that in the SNC, the ability of methamphetamine to the inhibit firing rate was comparable to its potency in the VTA. A marked difference in sensitivity between these sites has been reported for amphetamine (10, 11). According to these reports, a 50% inhibitory dose of amphetamine in the SNC and the VTA dopamine cells was
1.8 mg/kg and 0.5 mg/kg, respectively, in immobilized rats. In anesthetized rats, Bunney et al. (13) reported that when given in increasing incremental doses, the mean intravenous dose that inhibited the firing rate by 50% was 1.6 mg/kg in the SNC. On the other hand, Wang (16) reported that intravenous amphetamine markedly depressed dopamine cells in the VTA at a relatively low dose (ED50=0.62 mg/kg) in anesthetized rats. In the present study, the potency difference between the SNC and the VTA in producing 50% inhibition of dopamine cells activity to methamphetamine was only slight.

Peachey et al. (17) have reported that methamphetamine exerted greater central excitation in behaviour than amphetamine. In good agreement with this report, we found that the ability of methamphetamine to inhibit the firing rate of dopamine cells in the SNC and the VTA was much greater than that reported for amphetamine (10, 11, 13, 16). Methamphetamine was 5-6 times as potent as amphetamine in inducing 50% inhibition in the SNC and twice as potent as amphetamine in the VTA. It is conceivable that the methamphetamine-induced inhibition of dopaminergic activity in the SNC may be mediated either by a local release of DA from dendritic terminals or recurrent axon collateral (18) or by a feedback loop originating in the neostriatum (19). It is unclear at the present, however, why the inhibitory action by methamphetamine on the DA neuron is more potent than that of amphetamine. With respect to this, further investigation will be required to determine the mechanisms responsible for this difference in potency.

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