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Drugs Affecting Dopamine Neurons and Yawning Behavior

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MOGILNICKA, E. AND V. KLIMEK. *Drugs affecting dopamine neurons and yawning behavior.* PHARMAC. BIOCHEM. BEHAV. 7(4) 303–305, 1977. – Drugs stimulating the dopamine (DA) neurons in different ways (apomorphine, piribedil, amphetamine, nomifensine, L–DOPA) given in low doses (not producing behavioral excitation) induced yawning in rats. Blockade of DA receptors with neuroleptics counteracted DA-agonists induced yawning which may indicate a dopaminergic component of this behavior.

Dopamine agonists Dopamine antagonists Rat Yawning

THE INTRACEREBRAL injection of ACTH in mammals induces a peculiar syndrome characterized by stretching of the body and intensive yawning [3]. The secretion of the hypothalamic hormones (releasing and inhibiting factors) is regulated in large part neuronal circuits in the hypothalamus and adjacent areas of the brain and two of the principal transmitters in these circuits are noradrenaline (NA) and dopamine (DA) [8]. In rats apomorphine causes similar symptoms as ACTH does, therefore it seemed interesting to check this phenomenon more thoroughly. The effect of different DA agonists and antagonists was tested on rats in this respect.

METHOD

All experiments were performed on male albino Wistar rats weighing 180–260 g. Behavioral observations were made while the animals were individually housed in wire net cages at room temperature of 20–21°C. Food and water were withdrawn during behavioral observation. Number of yawnings were counted immediately after DA agonist administration during 0.5 hr period of time after apomorphine or piribedil or during 1 hr after d-amphetamine, nomifensine and L–DOPA.

The DA agonists were used in doses which did not produce behavioral stimulation. The neuroleptics were given before the DA agonists as follows: butaclamol 0.5 hr, spiperone 1 hr, pimozide 3.5 hr, reserpine 24 hr. All the DA agonists, except L–DOPA were injected subcutaneously as aqueous solution. L–DOPA IP as suspension in 1% Tween 80 was used together with a decarboxylase inhibitor (Ro 4–4602) given in a dose of 25 mg/kg IP, 0.5 hr before L–DOPA. α-Methyltyrosine methylester (α-MT) was injected IP 5 hr before DA agonists.

The statistical calculations were performed with the U-Whitney test, groups consisted of 10 rats. Data represent medians.

The following substances were used: d-amphetamine sulfate (Smith Kline & French), apomorphine HCl (Sandoz), butaclamol HCl (Ayerst Laboratories), L–DOPA (Reanal), α-methyltyrosine methylester (Sigma), nomifensine maleate (Hoe 984, Hoechst), pimozide (Janssen Pharmaceutica), piribedil (ET–495), Laboratoires Servier), reserpine (Serpasil, Ciba), Ro 4–4602 (N-D,L-α-seryl-N-(2,3,4-trihydroxybenzyl)-hydrazine hydrochloride, Hoffman-La Roche), spiperone (Janssen Pharmaceutica).

RESULTS

After small doses of DA agonists used (apomorphine, piribedil, amphetamine, nomifensine and L–DOPA) peculiar behavior, characterized by recurrent episodes of yawning, chewing and penile erection could be seen (Fig. 1). These effects began at approximately the same time for all drugs, i.e., 10–30 min after injection and lasted up to 30 min for apomorphine and piribedil and about 60 min for the rest of drugs used. Apomorphine, piribedil and L–DOPA were more effective than other drugs. Yawning appeared quickly with high frequency (mean value 10 episodes of yawning per 0.5 hr). After all drugs frequent grooming spells (performed with forelegs, hindlegs or head on the body) were seen during observation.

The yawning response produced by apomorphine was completely inhibited by spiperone (0.1 mg/kg), butaclamol (0.6 mg/kg) and pimozide (0.4 mg/kg) (Fig. 2). All the neuroleptics given alone did not induce yawning in doses used.

In rats injected with apomorphine (0.05 mg/kg) and pretreated with high dose of reserpine (7.5 mg/kg) yawning movements were reduced (Fig. 1); simultaneously stereotyped behavior consisting of continuous explorative sniffing was observed. Also α-MT (250 mg/kg) reduced significantly frequency of yawning after apomorphine but did not influence general behavior of rats. A similar effect (as α-MT) on apomorphine induced behavior was produced by combined treatment with reserpine and α-MT (Fig. 1). Neither reserpine, α-MT nor reserpine plus α-MT influenced markedly amphetamine induced yawning. Reserpine did not

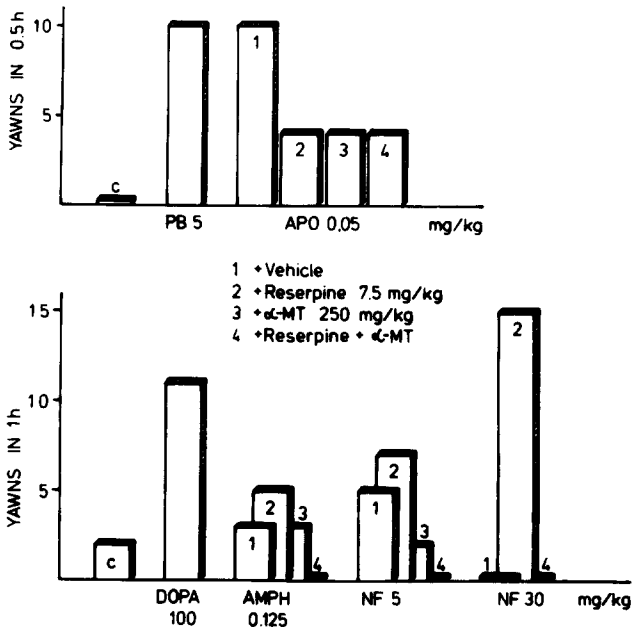

FIG. 1. Effect of dopamine agonists on yawning in normal and monoamines depleted rats. C, control animals injected with saline. PB, piribedil; APO, apomorphine; AMPH, amphetamine; NF, nomifensine. N for each group = 10. Statistical difference (U-Whitney Test): PB vs C, $p<0.01$; APO(1) vs C, $p<0.01$; DOPA vs C, $p<0.01$; AMPH(1), NF (5 mg/kg) (1), NF (30 mg/kg) (1) vs C, NS; 2, 3, 4 vs APO, $p<0.05$; 2, 3, 4 vs AMPH, NS; 2, 3 vs NF (5 mg/kg), NS; 4 vs NF (5 mg/kg), $p<0.05$; 2 vs NF (30 mg/kg), $p<0.01$. Other details in the text.

change frequency of yawning in nomifensine 0.5 mg/kg treated rats. Pretreatment with α–MT or reserpine plus α–MT counteracted the development of yawning caused by nomifensine. Nomifensine in a high dose (30 mg/kg) produced stereotyped behavior (sniffing, licking) but did not induce yawning. The pretreatment with reserpine counteracted nomifensine-induced stereotypy whereas frequent yawning was seen. The combined treatment with reserpine and α–MT prevented stereotypy as well as yawning caused by nomifensine (Fig. 1).

DISCUSSION

The present observations showed that drugs stimulating the DA neurons in different ways, given to the rats in low doses, not producing the typical symptoms of behavioral excitation (hypermotility, rearing, stereotypy), induced yawning often accompanied by penile erection. Yawning appeared after apomorphine and piribedil, drugs directly influencing DA receptors [2, 6, 7], amphetamine and nomifensine, drugs with DA releasing and DA uptake inhibiting properties as well as after L–DOPA, precursor of DA [9,10]. Frequency of yawning was much higher after apomorphine or piribedil when compared with the remaining drugs used. The yawning performance was antagonized by spiperone, pimozide, butaclamol, specific DA receptor blockers [1, 2, 11], used at smaller doses than those inducing catalepsy. These results suggest that the yawning activity may, at least, partly depend on dopaminergic component. Similar conclusions could be drawn from the results of experiments with partly or completely monoamines depleted rats. Reserpine and α-MT given together completely deplete DA from its nerve terminals and in such treated rats amphetamine and nomifensine did not induce yawning. It seems therefore that in DA agonists evoked yawning release of DA and inhibition of DA uptake displayed by these drugs may be of some importance. In the present study it was also found that pretreatment of rats with α-MT reduced apomorphine induced yawning. We have no explanation for this observation since apomorphine is supposed to act directly on DA receptors [2,7]. It seems also that for performance of yawning only minute DA-ergic stimulation is necessary. Doses of DA agonists higher than those used in our experiments provoke symptoms characteristic for strong stimulation of DA receptors. Nomifensine, acting via release of DA from reserpine sensitive pools [4], in 30 mg/kg produced stereotypy consisting of sniffing and licking. In the reserpinized rats the same dose induced intensive yawning instead of stereotypy, probably acting on newly synthesized DA. Carlsson *et al.* [5] suggested that DA agonists are able to activate two types of DA receptors (pre- and postsynaptic) resulting in behavioral inhibition and activation. It seems that apomorphine at the dose used in these experiments (0.05 mg/kg) influences mainly presynaptic DA receptors but some level of stimulation of postsynaptic DA receptors may occur too. In reserpine pretreated rats the DA receptor stimulation produced by apomorphine could be shifted more into direction of postsynaptic receptors, due to supersensitivity developed, and therefore it manifests in sniffing.

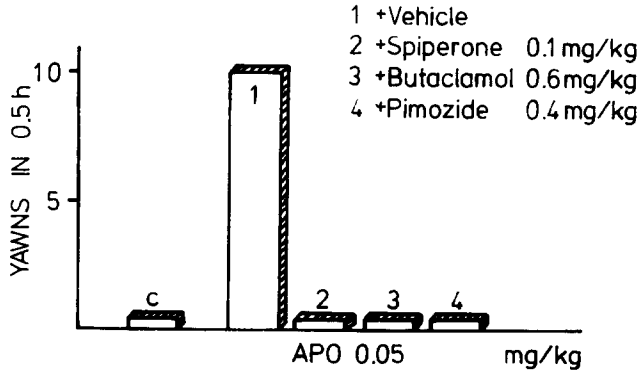

FIG. 2. Effect of apomorphine on yawning in normal and with blockade of central dopamine receptors rats. C, control animals injected with saline. APO, apomorphine (1). N for each group = 10. Statistical difference (U-Whitney Test): 1 vs C, $p<0.01$; 2, 3 vs 1, $p<0.01$; 4 vs 1, $p<0.05$. Other details in the text.

In conclusion, our results indicate that yawning appears after DA agonists and that blockade of DA receptors counteracts this effect. Obviously, more detailed studies will be needed before anything conclusive can be said about the exact nature of this phenomenon. Appearance of yawning may be useful in screening studies because it may indicate a dopaminergic component of action of investigated drugs.

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