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ON THE ACTIONS OF COMPOUNDS RELATED TO DOPAMINE AT A NEUROSECRETORY SYNAPSE

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1 The effects of a number of substances related to dopamine, including all its methylated derivatives, were investigated on the membrane potential and response to nerve stimulation of cockroach salivary gland cells.

2 Only *N*-methyldopamine (epinine), *N,N*-dimethyldopamine and *N,N*-dimethylnoradrenaline, all with unsubstituted hydroxyl groups, directly resembled dopamine in producing a hyperpolarization which could be as large as that caused by maximal nerve stimulation. During the continued presence of these substances the hyperpolarization waned and responses to nerve stimulation declined.

3 Many of the compounds caused one or both of two other effects, namely an increase in the rate of 'spontaneous miniature hyperpolarizations' and an enhancement of the submaximal responses to single nerve stimuli. There were no obvious structural requirements for these effects.

Introduction

Investigations of the pharmacology of dopamine-like substances have become of increasing interest in view of the likelihood that dopamine is a central neurotransmitter (see e.g. Hornykiewicz, 1966; Woodruff, 1971; Hornykiewicz, 1973; Vogt, 1973; Snyder, Banerjee, Yamamura & Greenberg, 1974; Iversen, 1975). However, the information obtained from the vertebrate central nervous system is in general somewhat indirect and it is evidently desirable to have available simpler systems in which physiological responses can be monitored directly. Several dopamine-sensitive preparations have recently been explored including the dog renal artery (see Goldberg, 1972) and certain ganglion cells in the mollusc (Woodruff & Walker, 1969; Ascher, 1972; Berry & Cottrell, 1975) and the guinea-pig (Hirst & Silinsky, 1975). A useful preparation may also be provided by the cockroach salivary gland (House, 1973) where there is growing evidence for dopaminergic transmission (Bland, House, Ginsborg & Laszlo, 1972; House, Ginsborg & Silinsky, 1973; Fry, House & Sharman, 1974; Ginsborg, House & Silinsky, 1974; Bowser-Riley & House, 1976) and this paper is concerned with the effects on that preparation of substances chemically related to dopamine.

The purpose of the work was first to obtain more information about the specificity of insect dopamine receptors, and secondly to explore the effects of a range of substances which might be formed from dopamine by metabolic processes. The substances investigated (which are listed in Table 1) include all the derivatives which result from methylation of the nitrogen and the oxygen atoms of dopamine. The experiments consisted in impaling acinar cells with a micro-electrode and observing the effect of the substance under test on the membrane potential and on the responses to nerve stimulation.

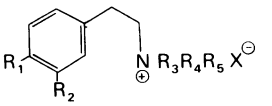
Methods

Compounds

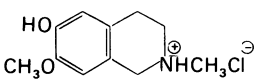
The amines tested (see Table 1) were generally crystallized as their hydrochloride salts from ethanol/ether and samples of 100–150 mg were analysed gravimetrically for halide. Melting points were recorded on a Mettler FP1 instrument at a heating rate of 0.2°C/minute.

Dopamine hydrochloride (1, Table 1) was obtained from Koch-Light and re-crystallized. 3-hydroxy-4-methoxyphenethylamine hydrochloride (2) was prepared from isovanillin by reaction with nitromethane to give the ω-nitro-styrene (Baxter, Allan & Swan, 1965) which was then reduced with lithium aluminium hydride (Fennoy, 1961). 4-Hydroxy-3-methoxyphenethylamine hydrochloride (3) was prepared by a similar method from vanillin. 3,4-Dimethoxyphenethylamine was obtained from Koch-Light and converted to its hydrochloride (4).

Table 1 Melting points and analyses of compounds



No.	*Trivial name*	R_1	R_2	R_3	R_4	R_5	X^-	*Melting-point (°C)*	X^- found	X^- calculated
1	Dopamine	OH	OH	H	H	H	Cl^-	242.7–243.5 (dec.)	18.61	18.69
2	4-Methyldopamine	OCH_3	OH	H	H	H	Cl^-	204.7–206.1	17.00	17.41
3	3-Methyldopamine	OH	OCH_3	H	H	H	Cl^-	212.1–213.0	17.27	17.41
4	3,4-Dimethyldopamine	OCH_3	OCH_3	H	H	H	Cl^-	153.5–154.2	16.25	16.29
5	Epinine	OH	OH	CH_3	H	H	Br^-	166.4–167.2	31.98	32.21
6	4-Methylepinine	OCH_3	OH	CH_3	H	H	Cl^-	156.3–158.2	16.51	16.29
7	3-Methylepinine	OH	OCH_3	CH_3	H	H	Cl^-	162.6–163.7	16.18	16.29
8	3,4-Dimethylepinine	OCH_3	OCH_3	CH_3	H	H	Cl^-	138.2–138.7	15.20	15.30
9	*N,N*-Dimethyldopamine	OH	OH	CH_3	CH_3	H	Cl^-	123.2–125.0	16.16	16.29
10	4-Methyl-*N,N*-dimethyldopamine	OCH_3	OH	CH_3	CH_3	H	Cl^-	161.1–162.7	15.24	15.30
11	3-Methyl-*N,N*-dimethyldopamine	OH	OCH_3	CH_3	CH_3	H	Cl^-	189.0–190.5	15.23	15.30
12	3,4-Dimethyl-*N,N*-dimethyldopamine	OCH_3	OCH_3	CH_3	CH_3	H	Cl^-	192.0–193.6	14.32	14.43
13	Coryneine (*N,N,N*-trimethyldopamine)	OH	OH	CH_3	CH_3	CH_3	I^-	204.7–205.0 (dec.)	39.22	39.27
14	4-Methyl-*N,N,N*-trimethyldopamine	OCH_3	OH	CH_3	CH_3	CH_3	I^-	215.5–215.9 (dec.)	37.35	37.63
15	3-Methyl-*N,N,N*-trimethyldopamine	OH	OCH_3	CH_3	CH_3	CH_3	I^-	*ca.* 187–190.8	37.57	37.63
16	3,4-Dimethyl-*N,N,N*-trimethyldopamine	OCH_3	OCH_3	CH_3	CH_3	CH_3	I^-	229.4–230.2	36.11	36.13
17	Methyl-*m*-tyramine	H	OCH_3	H	H	H	Br^-	126.4–127.5	34.45	34.42
18	*N,N*-Dimethyl-*m*-tyramine	H	OH	CH_3	CH_3	H	Cl^-	159.5–162.0	17.34	17.58
19	Methyl-*N,N*-dimethyl-*m*-tyramine	H	OCH_3	CH_3	CH_3	H	Cl^-	133.1–134.1	16.34	16.44
20	Hordenine	OH	H	CH_3	CH_3	H	Cl^-	169.0–170.7	16.75	17.58
21	Methyl-hordenine	OCH_3	H	CH_3	CH_3	H	Cl^-	173.5–175.6	16.41	16.44
22	Hordenine methiodide	OH	H	CH_3	CH_3	CH_3	I^-	226.5–227.1	41.28	41.31



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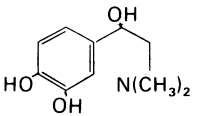
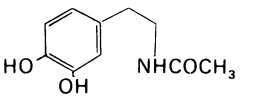


N,N-dimethylnoradrenaline
24



N-acetyldopamine
25

Difficulty was encountered in reducing the *N*-methyl amide of homoveratric acid with lithium aluminium hydride to give epinine (3,4-dihydroxyphenethylmethylamine, *N*-methyl dopamine); the ethyl ester was therefore reduced to the corresponding alcohol, which was converted to the chloride with phosphorus trichloride. Treatment with methylamine and demethylation with hydrobromic acid then gave epinine hydrobromide (5). For 3-hydroxy-4-methoxy- and 4-hydroxy-3-methoxy-phenethylmethylamine hydrochlorides (6 and 7) isovanillin and vanillin, respectively, were first protected by benzylation (Baxter *et al.*, 1965) converted to their ω-nitrostyrenes and reduced with lithium aluminium hydride to the primary amines. These were then converted to the *N*-monomethyl compounds by reaction with benzaldehyde, *N*-methylation with dimethyl sulphate and hydrolysis of the benzal group (Kirkwood & Marion, 1950). Finally, the benzyl group was removed by hydrogenolysis.

3,4-Dihydroxyphenethyldimethylamine hydrochloride (9) was obtained from homoveratric acid. The acid was converted to its chloride, which was reacted with dimethylamine and the resulting dimethylamide was reduced with lithium aluminium hydride. For 3-hydroxy-4-methoxy- and 4-hydroxy-3-methoxy-phenethyl-dimethylamine hydrochlorides (10 and 11), the protected primary amines prepared from isovanillin and vanillin (see above) were methylated with formaldehyde and formic acid (Moore, 1962). The products, however, included some tetrahydroisoquinoline derivatives formed by Pictet-Spengler ring closure, which were difficult to separate completely from the required products. This difficulty was avoided by carrying out the methylation reaction on 3-benzyloxy-4-methoxyphenethylmethylamine and its isomer, prepared above.

The quaternary derivative of dopamine, 3,4-dihydroxyphenethyl-trimethyl ammonium (13), was prepared by reaction of homoveratrylamine with methyl iodide followed by demethylation with hydriodic acid. The corresponding 4-methoxy and 3-methoxy compounds (14 and 15) were prepared by reaction of the tertiary base, in dry ether, with methyl iodide.

The tetrahydroisoquinoline obtained by Pictet-Spengler cyclisation of 3-benzyloxy-4-methoxyphenethylamine, presumably (after hydrogenolysis) 6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (23), had m.p. 260.8–261.4°C, and contained 15.43% Cl^- (calculated content = 15.43%).

1-(3,4-Dihydroxyphenyl)-2-dimethylaminoethanol (*N,N*-dimethyl-noradrenaline, (24)) was prepared from catechol. Chloroacetylation (Fellman, 1957) followed by reaction with dimethylamine and reduction with sodium borohydride (Chapman, Clarke & Harvey, 1971) gave the required product which was crystallized as the free amine, m.p. 138.2–138.4°C (dec) (lit. value 142–3°C, La Manna & Campiglio, 1960).

N-acetyldopamine (25) was prepared from protocatechualdehyde, which was protected by benzylation and converted to the ω-nitro-styrene (Baxter *et al.*, 1965). Reduction with lithium aluminium hydride gave 3,4-dibenzyloxyphenethylamine which was isolated as its hydrochloride. Acetylation of the free amine followed by removal of the benzyl groups by hydrogenolysis gave an oil which could not be crystallized but which was homogenous on silica gel thin-layer chromatography.

Preparation

Salivary glands, together with their ducts, (in which the nerves are embedded) and reservoirs were dissected from the cockroach *Nauphoeta cinerea* Olivier. The glands were spread across a pedestal in a perspex bathing chamber of 4 ml capacity. The ducts were drawn into a suction electrode for stimulation of the encapsulated nerves. Microelectrodes were filled with 3 M KCl and had resistances from 10–30 MΩ. The output of a preamplifier (W.P. Instruments) was fed in parallel to a Gould-Brush 220 pen recorder and a Tektronix Model 565 cathode-ray oscilloscope. The records shown are photographs of pen recorder traces.

The normal bathing solution contained (mM) NaCl 160, $CaCl_2$ 5, KCl 1, $NaHCO_3$, 1 and NaH_2PO_4, 1 and was supplied to the preparation continuously at a rate of 2 ml/min by a Watson Marlow flow inducer and removed at the same rate by suction. Drugs were applied by changing the delivery tube of the flow inducer from the control to the drug solution and briefly increasing the flow rate to about 20 ml/minute.

Responses

The main features have already been described (House, 1973) but it may be convenient for the reader to have a brief account here. The response to nerve stimulation occurs after a delay of about 1 s and consists of a hyperpolarization whose amplitude and duration are graded with the strength and number of stimuli, sometimes followed by a small depolarization. In this investigation we have been concerned only with the hyperpolarization. The stimuli were of 0.5 ms duration and at a frequency of 90 hertz. Responses of maximal amplitude required up to 20 stimuli at 40 volts. The responses were approximately constant if the bursts of stimuli were repeated not more frequently than 1 per 2 minutes.

Results

Direct action on membrane potential

Each of the 25 compounds listed in Table 1 was tested on at least 2 preparations in concentrations of up to

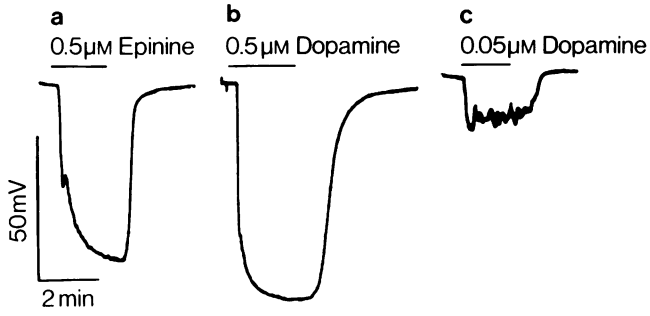


Figure 1 Hyperpolarizations recorded intracellularly from a cockroach salivary gland in response to epinine (0.5 μM) in (a) and dopamine (0.5 μM) in (b) and (0.05 μM) in (c) (same impalement). The periods in which the drug containing solutions flowed through the bath, replacing the flowing control solution (see methods section), are indicated by the lines above each trace.

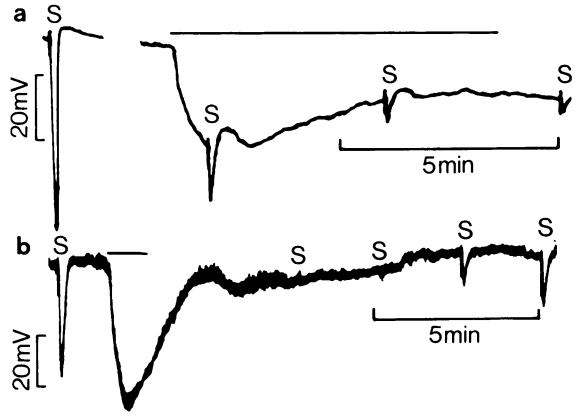


Figure 2 Waning of hyperpolarization and reduction of responses to nerve stimulation. Records from two different experiments in which *N,N*-dimethyl dopamine was admitted to the chamber in concentration of 0.4 μM (a) and 2 μM (b). The periods during which the drug solution was present are indicated by the lines above the traces. Bursts of nerve stimuli indicated by S: in (a) each burst consisted of 10 stimuli at 50 V (0.5 ms, 90 Hz) and in (b), of 4 stimuli at 20 V (0.5 ms, 90 Hz).

and including 10 μM, which is of the order of 100 times the concentration of dopamine needed for a half maximal response. Only 4 compounds brought about a hyperpolarization similar to that produced by a burst of nerve stimuli. These were dopamine (see also House *et al.*, 1973), epinine, *N,N*-dimethyldopamine, and, like noradrenaline (see Bland *et al.*, 1972), *N,N*-dimethylnoradrenaline. Thus from a structure activity point of view it appears that dopamine-like activity on the cockroach salivary gland survives mono- or di-methylation of the nitrogen atom but requires both unsubstituted catechol hydroxyl groups. Their presence is evidently however insufficient to produce dopamine-like activity, since *N*-acetyl-dopamine (a metabolite thought to be of greater importance in insects than in mammals, see Fänge & Hanson, 1973) is inactive.

Figure 1 illustrates the action of epinine and shows that its potency is somewhat less than that of dopamine (perhaps about one third). The potency of *N,N*-dimethyldopamine was found to be about the same as that of epinine, but more exhaustive experiments would be required to obtain reliable values.

Reduction of response to nerve stimulation

Figure 2 illustrates another effect of substances which cause hyperpolarization. During prolonged exposure to *N,N*-dimethyl-dopamine (Figure 2a), or even during short exposure to high concentrations (Figure 2b), the hyperpolarization gradually waned and the responses to nerve stimulation were reduced in amplitude

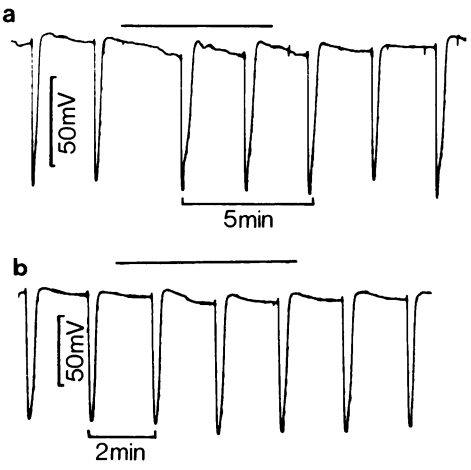


Figure 3 Absence of inhibitory effect on responses to maximal nerve stimulation. In (a) the responses are to bursts of 10 stimuli (0.5 ms, 90 Hz, 40 V); solution containing 20 μM coryneine admitted during period indicated by line above trace. In (b) responses were to 5 stimuli (0.5 ms, 90 Hz and 20 V) and the drug solution contained 20 μM 3-methyl-*N,N*-dimethyldopamine.

(Figure 2a) or sometimes even temporarily abolished (Figure 2b). Similar results have been obtained with all the hyperpolarizing substances so far tested on this preparation.

Absence of antagonist action

Apart from the action of the agonists described in the previous section, no other compounds had any blocking effect on the responses to nerve stimulation. Two experiments to test this point are illustrated in Figure 3. Bursts of stimuli were applied to the salivary nerves at regular intervals, the stimulus strength being chosen so that the responses were of maximal amplitude. In the experiment of Figure 3a the preparation was exposed to 20 μM coryneine (13, Table 1) and in 3b, to 20 μM 3-methyl-*N,N*-dimethyldopamine (11, Table 1): in neither case was there any reduction in response. Similar results were obtained with all the compounds of Table 1, except those causing hyperpolarization.

Enhancement of spontaneous activity

It has been reported by House (1973) that spontaneous electrical activity may occasionally be recorded from unstimulated salivary gland cells. This has the appearance of a random sequence of small hyperpolarizations (which have been referred to as miniature secretory potentials) varying in amplitude but similar in time course to the larger hyperpolarizations which result from nerve stimulation. In previous investigations, a number of substances (e.g. bretylium, Silinsky, 1974; tyramine, Ginsborg, House and Silinsky, unpublished observations) have been found to enhance this activity, and it has been tentatively suggested that these substances do so by promoting the release of packets of the neurotransmitter from the salivary nerve terminals. Several of the compounds of the present series enhanced spontaneous activity. The effect appears to be somewhat variable, perhaps because it depends on the particular state of the nerve terminals which may vary in a way not controlled experimentally. Figure 4 illustrates the effect of 10 μM *N,N*-dimethyl-*m*-tyramine from an experiment on a particularly responsive preparation. Other substances which enhanced spontaneous activity were 3-methylepinine, 3-methyl-*N,N,N*-trimethyldopamine and hordenine (7, 15 and 20, Table 1). It seems possible that the hyperpolarizing substances also produce this kind of activity superimposed on their direct effect; this would account for the increased 'noise' recorded during the responses to their application, especially where, as in Figure 1c for example, the responses are small, and the membrane potential distant from the equilibrium potential for the action of the agonist (see Ginsborg *et al.*, 1974).

Potentiation of submaximal responses

As was mentioned in the Methods section, it is generally necessary to apply a short burst of stimuli to the salivary nerve to produce a maximal hyperpolarization of the gland cells. With single stimuli submaximal responses occur: these have been found to be enhanced by many of the substances of the present series. Figure 5 illustrates the action of the quaternary derivative, coryneine (13, Table 1). Shortly after the control bathing solution was changed to one containing the drug, in a concentration of 10 μM, the responses to single stimuli increased in amplitude. In the experiment of Figure 5a, the enhanced response corresponded to that produced by a burst of between 3 and 4 stimuli in the control solution, and in 5b to that produced by 2 stimuli. It must be noted that the effect, like that of the enhancement of spontaneous activity described above, was variable. For example, in one experiment 10 μM coryneine had no effect although in three other similar experiments an unequivocal potentiation occurred.

The following compounds were observed to cause a potentiation at a concentration of 10 μM such that a single stimulus caused a response at least equivalent to that produced by two stimuli in the control solution: *dopamine derivatives:-* 3-methyl, 4-methyl; *epinine derivatives:-* 4-methyl, 3,4-dimethyl; N,N-*dimethyldopamine derivatives:-* 3-methyl, 3,4-dimethyl;

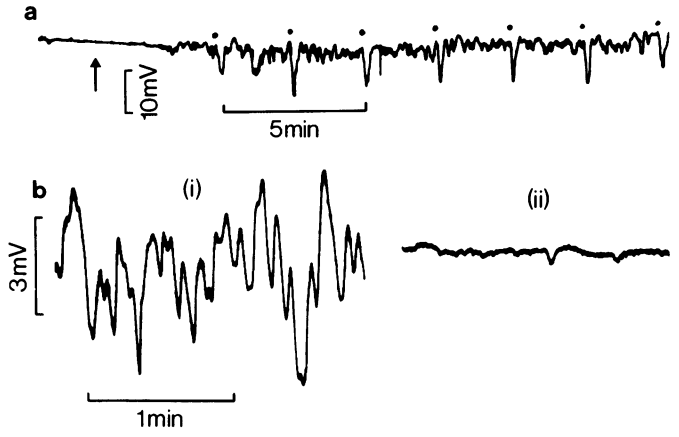


Figure 4 Enhanced spontaneous activity caused by 10 μM *N,N*-dimethyl-*m*-tyramine. In (a) the drug solution was admitted at the arrow. The symbol (●) above the trace indicates response to single stimuli (0.5 ms, 60 V). In (b) (i) from a different cell in the same preparation, the effect of 10 μM *N,N*-dimethyl-*m*-tyramine at higher amplification is shown; (ii) was recorded 10 min after the control solution was reinstated.

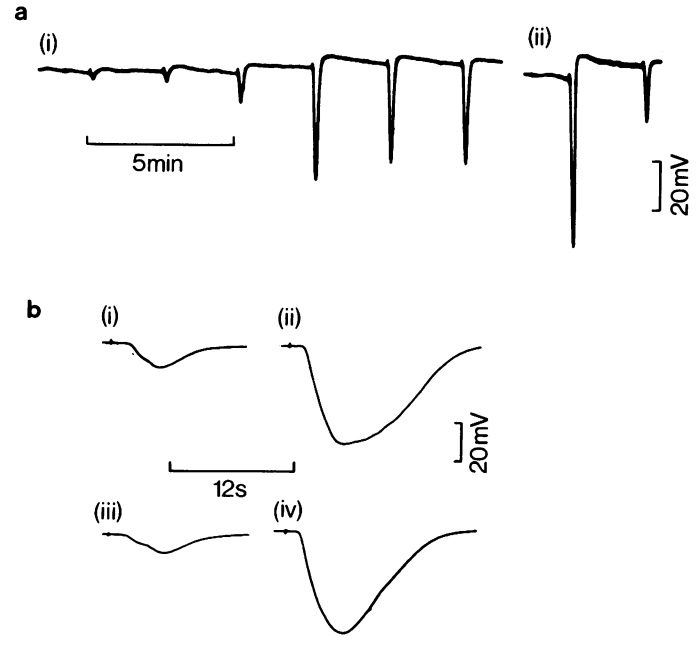


Figure 5 Effect of 10 μM coryneine on the responses to single stimuli. Two different preparations. In (a) (i) the responses are to 6 successive single stimuli of 15 volts. The drug solution was admitted immediately before the second stimulus. In (ii) responses after a prolonged wash in control solution to bursts of 4 and 3 stimuli respectively are shown. In (b), control responses to single stimuli of 10 V are shown in (i) and (iii); (ii) is the response to a single stimulus in 10 μM coryneine and (iv) the response to 2 stimuli in the control solution.

N,N,N-*trimethyldopamine and derivatives:-* coryneine, 3-methyl, 4-methyl, 3,4-dimethyl; *hordenine methiodide.* There are no obvious structural requirements: furthermore, because of the small number of experiments made with each compound (usually 2 or 3) it cannot be confidently assumed that the unlisted ones are necessarily always without effect.

Discussion

Three kinds of effect have been described in the preceding results. First are the hyperpolarizations which can be as large as those produced by maximal nerve stimulation. They are presumably due to a direct action on 'dopamine receptors' leading to an increase in potassium conductance (Ginsborg *et al.,* 1974). Such effects were produced only by those compounds with unsubstituted hydroxyl groups. This seems to be a general requirement for the retention of dopamine-like activity in simple dopamine analogues in a variety of situations (Goldberg, Sonneville & McNay, 1968; Woodruff & Walker, 1969; Sheppard & Burghardt, 1974; Miller, Horn, Iversen & Pinder, 1974; Costall, Naylor & Pinder, 1974) summarized in Table 2.

The second and third effects are an increase in the frequency of the small intermittent hyperpolarizations which occur spontaneously and the enhancement of responses to nerve stimulation. It may tentatively be suggested that they represent respectively enhancement of the spontaneous release of the neurotransmitter and an enhancement of its release by nerve stimulation (cf. Von Voigtlander & Moore, 1973). It must however be stressed that there is no direct evidence relating to these suggestions and that experiments of a different kind will be required to test them. A post-synaptic effect cannot at present be ruled out. On the assumption that the present results are relevant to the central nervous system, it is of interest to consider their possible bearing on the theories which attribute certain psychoses to abnormal metabolites (see e.g. Ernst, 1965) which over-stimulate dopaminergic systems (see e.g. Snyder *et al.,* 1974; Matthysse & Lipinski, 1975). Of the three possible forms of stimulation which might be produced by methylated dopamine metabolites, it seems unlikely that the direct effect of the *N*-methylated derivatives would be of importance, since a persistent concentration of either would inhibit the effect of dopaminergic nerve stimulation (see Figure 2). Furthermore they would presumably be subject to the normal enzymatic de-activation process of 3-methylation. However many of the 3-methylated derivatives produce the two effects that appear to enhance dopaminergic activity and might therefore be harmful.

We are greatly indebted to Dr R.B. Barlow for much help and advice. K.W.T. was a Mental Health Trust and Research Fund Fellow. Animal accommodation was provided by the Wellcome Research Unit.

Table 2 Comparison of effects of various dopamine analogues in different tests

	Test situation and reference	*Substances tested, also tested in this paper*	*Effect*	*Effect this paper* D = dopamine-like
1	Renal vasodilatation (Goldberg *et al.,* 1968)	Epinine	D	D
		N,N-dimethyldopamine	–	D
		3-Methyldopamine	–	–
		4-Methyldopamine	–	–
2	Inhibition in snail brain (Woodruff & Walker, 1969)	Epinine	D	D
		3-Methyldopamine	–	–
		3,4-Dimethyldopamine	–	–
3	Activation of dopamine-sensitive adenylate cyclase from rat brain (Miller *et al.,* 1974)	Epinine	D	D
		N,N-dimethyldopamine	D	D
		Coryneine	D	–
		3-Methyldopamine	–	–
		4-Methyldopamine	–	–
	(Sheppard & Burghardt, 1974)	Epinine	D	D
		N,N-dimethyldopamine	D	D
		Coryneine	–	–
4	Behaviour changes in the rat (Costall *et al.,* 1974)	Epinine	D	D
		N,N-dimethyldopamine	D	D
		3-methyldopamine	–	–
		4-methyldopamine	–	–

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