Br. J. Pharmac. (1975), 55, 351-358

BEHAVIOURAL CHANGES INDUCED IN CONSCIOUS MICE BY INTRACEREBROVENTRICULAR INJECTION OF CATECHOLAMINES, ACETYLCHOLINE AND 5-HYDROXYTRYPTAMINE

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1 A simple method of injecting soluble substances into the lateral ventricle of the brain of the conscious mouse is described.

2 The effect of various doses of noradrenaline, dopamine, acetylcholine, 5-hydroxytryptamine given into the right lateral brain ventricle were tested on locomotor and exploratory activities of mice.

3 Noradrenaline in a dose of 0.1 μg increased locomotor activity. This effect was prevented by phenoxybenzamine but not by propranolol.

4 Higher doses of noradrenaline (1 or 10 μg) decreased locomotor and exploratory activities. Propranolol but not phenoxybenzamine abolished these effects.

5 Dopamine (0.1 or 1 μg) increased locomotor activity. The higher doses also induced tremor.

6 The highest dose of dopamine tested (10 μg) elicited stereotypical behaviour.

7 All the behavioural phenomena induced by 0.1 μg and 10 μg of dopamine were blocked by pimozide.

8 Acetylcholine (1 and 10 μg) and 5-hydroxytryptamine (1 μg) inhibited locomotor and exploratory activity.

9 The effects of 1 and 10 μg of acetylcholine were abolished by atropine (5 mg/kg i.p.). Methysergide (5 mg/kg i.p.) had no influence on the effects of 5-hydroxytryptamine (1 μg).

Introduction

In the last 25 years several authors have studied the behavioural effects of biogenic amines. These amines have been injected intraventrically, intracisternally, and into various brain structures in order to circumvent the blood-brain barrier. Adrenaline, noradrenaline (NA) and dopamine have been shown to depress a variety of different types of behaviour in dogs, cats, chickens, sheep, monkeys and rats (Leimdorfer, 1950; Feldberg & Sherwood, 1954; Palmer, 1959; Schain, 1961; Wada, 1962; Traczyk, 1964; Marley & Stephenson, 1969, 1970; Grunden & Marley, 1970). Amongst the changes observed by these authors were decreased locomotor activity, stupor, sleepiness, anaesthesia, catalepsy and sleep.

Other authors have described behavioural activation in rats after intraventricular administration of NA or dopamine (Segal & Mandell, 1970; Malec & Kleinrok, 1972; Stern & Zwick, 1973) or after intrahypothalamic or intrastriatal NA or dopamine injection (Benkert & Köhler, 1972). In this laboratory it has been shown that lower doses of NA applied intraventricularly cause increased locomotor activity in rats, but that higher doses elicit a stuporous syndrome. It has also been shown that the excitatory effects of NA in rats are dependent upon normal genetically determined exploratory activity (Herman, 1970). 5-Hydroxytryptamine (5-HT) and acetylcholine (ACh) decreased locomotor activity in rats, when injected intraventricularly (Herman, Kmieciak-Kołada, Słomińska-Żurek & Szkilnik, 1972; Herman, 1973).

The present experiments attempted to answer two questions: are the behavioural effects of NA, dopamine, ACh and 5-HT in mice similar to those described in rats; and are these effects pharmacologically specific?

Methods

The experiments were carried out on male, white, Swiss mice, weighing 20 g, 1 month old supplied by the Central Animal Farm of the Silesian School of Medicine.

Drugs

Noradrenaline bitartrate (Sigma), dopamine hydrochloride (Sigma), acetylcholine iodide (Chemapol), and 5-hydroxytryptamine (serotonin creatinine sulphate, Koch-Light) were injected intracerebroventricularly (i.c.v.). Pimozide (Janssen) was administered intraperitoneally. Doses of these substances are expressed as free bases.

Phenoxybenzamine hydrochloride (Smith Kline & French), propranolol hydrochloride (ICI), methysergide dimaleate (Deseril, Sandoz) and atropine sulphate (Polfa) were injected intraperitoneally. Doses of these substances were dissolved in 0.9% w/v NaCl solution (saline), except for methysergide, which was obtained from ampoules of Deseril.

Intraventricular injection technique

Mice were prepared as follows. Under light ether anaesthesia an incision was made along the mid-line of the skull. The bones were cleaned of connective tissue and the superior and transverse venous sinuses were identified. A point 3 mm from the confluence of the two sinuses and from the sagittal sinus of the right side was found. Here a small hole in the skull was made with an intramuscular needle with a sharp end. The hole was made by rotary movements of the needle. Twenty-four hours after this operation an intraventricular injection was performed using a 25 gauge needle with a sharp (17°) point, attached to a 1 μl Hamilton microsyringe 7001 N fixed to a stand, which allows vertical movements of the syringe. The plastic tube covered the whole needle except for the terminal 3 mm. The needle was left in place for approximately 10 s after injection. The procedure was checked by injection of 1 μl of methylene blue solution into the right lateral ventricle of the brain in 100 mice each weighing 20 grams. The place of puncture was examined and the presence of dye in the lateral ventricles was looked for by means of a hand lens after the animal had been killed and the brain sectioned. Of the injections, 8% were found not to have entered the ventricle. In these animals ataxic movements and head turning were observed. In the course of experiments if these behavioural changes suggested a faulty injection, the point of puncture and the walls of the lateral ventricle were examined macroscopically. If damage was observed in the tissues around the ventricle, the results obtained in these animals were discarded.

Observation of behaviour

Each mouse was placed in a glass cage, dimensions 40 x 25 x 25 cm, for 10 minutes. During this period the amount of time spent walking, washing, sniffing and in immobility was measured in seconds with a stop-watch to the nearest 1 second. These types of behaviour were classified as locomotor activity. The duration of tremors and stereotyped movements of the head were measured when these phenomena appeared. The number of rearings was also counted; rearing was considered as an exploratory activity.

Experimental design

Biogenic amines were dissolved in freshly prepared saline (0.9% w/v NaCl solution) a few seconds before the intraventricular injection. One mouse was injected with one dose of biogenic amine in the volume of 1 μl, the second animal with 1 μl of saline. The behaviour of both mice was measured immediately after intracerebroventricular injection. In a second series of experiments antagonists of biogenic amines were injected intraperitoneally in saline in a volume of 1 ml/kg. One hour later the behaviour of the animals was observed either after the antagonist alone or after intraventricular injection of biogenic amine. In other experiments the behavioural phenomena were measured in intact animals and compared with those seen in intraventricularly sham-injected mice and in animals injected intraventricularly with saline. Finally some groups of animals were injected intraventricularly with NA and immediately afterwards with dopamine. All mice were used only once. All experiments were performed between 09 h 00 min and 12 h 00 min during a period of 1.5 years. The statistical significances of the changes observed were assessed by Student's *t*-test.

Results

Doses of substances blocking the pharmacological effects of biogenic amines used in these experiments did not affect the components of behaviour of mice assessed. Pimozide in a dose of 0.1 mg/kg was an exception and was not used in this dose in further experiments (Table 1).

NA (0.1 μg i.c.v.) increased walking time and decreased immobility. These effects were

Table 1 Behaviour of mice after injections of drugs blocking pharmacological effects of biogenic amines

Control	Time (s)				Number of rearings	Drug (mg/kg i.p.)	Time (s)				Number of rearings
	Walking	Cleaning	Sniffing	Immobility			Walking	Cleaning	Sniffing	Immobility	
Saline 0.9% (1 ml/kg of body weight i.p.)	200 ± 13.4	30 ± 7.1	25 ± 5.0	345 ± 15.5	10 ± 1.8	Phenoxybenzamine (5)	210 ± 15.6 $P > 0.35$	35 ± 10.1 >0.35	25 ± 5.1 >0.4	320 ± 15.4 >0.05	7 ± 1.2 >0.15
	230 ± 34.2	60 ± 15.3	35 ± 6.7	275 ± 28.3	16 ± 4.4	Propranolol (10)	238 ± 22.5 $P > 0.4$	62 ± 12.5 >0.45	40 ± 7.1 >0.3	260 ± 27.7 >0.4	16 ± 2.7 >0.35
	230 ± 19.0	45 ± 7.4	20 ± 4.2	305 ± 19.3	21 ± 2.0	Pimozide (0.05)	240 ± 26.7 $P > 0.3$	30 ± 8.0 >0.1	30 ± 6.8 >0.1	300 ± 27.7 >0.4	24 ± 3.7 >0.25
	290 ± 21.1	40 ± 10.4	20 ± 3.0	250 ± 21.6	32 ± 2.1	Pimozide (0.1)	230 ± 24.7 $P > 0.05$	20 ± 6.3 >0.05	10 ± 2.5 <0.025	340 ± 24.6 <0.0125	28 ± 2.9 >0.15
	210 ± 33.7	50 ± 11.1	25 ± 3.0	315 ± 45.7	13 ± 1.7	Methysergide (5)	240 ± 40.2 $P > 0.25$	50 ± 8.1 >0.5	30 ± 4.2 >0.15	280 ± 41.2 >0.25	20 ± 4.4 >0.05
	380 ± 13.8	20 ± 4.8	10 ± 3.3	190 ± 10.7	32 ± 5.8	Atropine (5)	340 ± 25.8 $P > 0.1$	30 ± 15.7 >0.25	10 ± 3.3 >0.5	220 ± 21.0 >0.15	40 ± 5.8 >0.2

n = 10 in each group. Results expressed as a mean ± s.e.

abolished by phenoxybenzamine (5 mg/kg i.p.) but not by propranolol (10 mg/kg i.p.). A higher dose of NA (1 μg) decreased walking and cleaning and abolished the sniffing and rearings, and increased immobility. Phenoxybenzamine did not change these effects. Propranolol reversed the behavioural effects of this dose of NA. The highest dose of NA (10 μg) caused complete immobility of mice. Phenoxybenzamine did not affect this phenomenon. Propranolol inhibited it (Table 2).

Dopamine (0.1 μg) increased the time spent walking and cleaning and the number of rearings and decreased the time spent immobile. These effects of dopamine were inhibited by pimozide. Dopamine in a dose of 1 μg increased the time of walking, decreased the time of immobility and induced tremors. Pimozide blocked these phenomena. After a dose of 10 μg of dopamine stereotyped movements of the head were observed. This type of behaviour was blocked by pimozide (Table 3).

Sham intraventricular injection caused a significant decrease in walking time. Intracerebroventricular injection of saline caused a decrease in walking time, in the number of rearings, and an increase in time spent immobile (Table 4). Simultaneous injections of NA and dopamine (0.1 μg) increased walking time and sniffing, and decreased immobility. The higher dose (1 μg) of both catecholamines administered i.c.v. simultaneously caused a decrease of walking time and of the number of rearings, suppressed cleaning and increased the time spent in sniffing and immobility (Table 4).

ACh in a dose of 0.1 μg increased the time spent sniffing and in a dose of 1 μg decreased walking time and increased the time spent immobile. The same effects, together with a decrease in time spent sniffing and suppression of rearing, were observed after a dose of 10 μg of ACh. These effects of ACh were abolished by atropine (Table 5).

5-HT in a dose of 0.1 μg caused no changes in behaviour but in a dose of 1 μg decreased walking time, suppressed cleaning and rearing, and increased the time spent immobile. Methysergide had no influence on these effects of 5-HT (Table 6).

Discussion

The results presented show that sham intracerebroventricular injection or injection of saline to conscious mice depress both locomotor and exploratory activity. Therefore in interpreting the behavioural effects of intraventricularly injected substances the fact that the results are

Table 2 Behavioural effects of noradrenaline (NA) in mice

	Group											
	I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*
Component of behaviour	*Saline (control)*	*NA (0.1 μg)*	*Pb (5 mg/kg) plus NA (0.1 μg)*	*Prop (10 mg/kg) plus NA (0.1 μg)*	*Control*	*NA (1 μg)*	*Pb (5 mg/kg) plus NA (1 μg)*	*Prop (10 mg/kg) plus NA (1 μg)*	*Control*	*NA (10 μg)*	*Pb (5 mg/kg) plus NA (10 μg)*	*Prop (10 mg/kg) plus NA (10 μg)*
Walking (s)	45 ± 12.4	95 ± 11.8 *P* I/III <0.01	50 ± 10.0 *P* II/III <0.01	100 ± 9.7 *P* II/IV >0.5	153 ± 32	59 ± 12 *P* V/VI <0.025	50 ± 12 *P* VI/VII >0.5	110 ± 10 *P* VI/VIII <0.01	141 ± 23	0	0	110 ± 16
Cleaning (s)	10 ± 4.4	25 ± 8.3 >0.05	0	15 ± 4 >0.2	53 ± 23	15 ± 3 <0.025	10 ± 33 >0.3	40 ± 6 <0.005	45 ± 20	0	0	20 ± 6
Sniffing (s)	5 ± 2.6	15 ± 4.7 >0.05	10 ± 5 >0.2	5 ± 2 >0.05	20 ± 9	0	10 ± 4	10 ± 3	48 ± 17	0	0	0
Immobility (s)	540 ± 10.3	465 ± 17.2 <0.0005	540 ± 21 <0.01	480 ± 8 >0.5	374 ± 60	526 ± 16 <0.025	530 ± 12 >0.5	440 ± 9 <0.0005	366 ± 40	600 ± 0 *P* IX/X <0.0005	600 ± 0	470 ± 15 *P* X/XII <0.0005
Number of rearings	2 ± 0.6	4 ± 1.0 >0.1	0	3 ± 1 >0.1	2 ± 1	0	2 ± 1	3 ± 1	2 ± 0	0	0	2 ± 1

n = 10, except groups I, II where n = 20. Results expressed as a mean ± s.e.
Pb = phenoxybenzamine; Prop = propranolol.

Table 3 Behavioural effects of dopamine (DA) in mice

Component of behaviour	*Group I* Saline control	*II* DA (0.1 μg)	*III* Pim (0.05 mg/kg) plus DA (0.1 μg)	*IV* Control	*V* DA (1 μg)	*VI* Pim plus DA (1 μg)	*VII* Control	*VIII* DA (10 μg)	*IX* Pim plus DA (10 μg)
Walking (s)	42 ± 7	124 ± 14 *P* I/II <0.0005	70 ± 15 *P* II/III <0.01	70 ± 14	115 ± 20 *P* IV/V <0.05	84 ± 21 *P* V/VI >0.2	85 ± 30	120 ± 25 *P* VII/VIII >0.2	100 ± 25 *P* VIII/IX >0.3
Cleaning (s)	0	6 ± 3 <0.05	6 ± 3	10 ± 4	8 ± 3	45 ± 15 <0.02	15 ± 5	0	3 ± 2
Sniffing (s)	11 ± 5	16 ± 6 >0.3	16 ± 5	20 ± 5	36 ± 10	44 ± 11	20 ± 10	7 ± 4 >0.15	11 ± 5
Tremor (s)	0	0	0	0	161 ± 34	0	0	0	0
Immobility (s)	546 ± 6	453 ± 20 <0.0025	508 ± 15 <0.05	500 ± 10	280 ± 42 <0.0005	470 ± 20 <0.0002	480 ± 20	360 ± 34 <0.01	476 ± 28 <0.02
Stereotyped movements of the head	0	0	0	0	0	0	0	115 ± 28	0
Number of rearings	1 ± 0	3 ± 1	1 ± 0	1 ± 0	2 ± 0	0	2 ± 1	2 ± 1	2 ± 1

n = 10. Results expressed as a mean ± s.e.
Pim = pimozide.

Table 4 Behavioural effects of noradrenaline (NA) and dopamine (DA) injected simultaneously intraventricularly (i.c.v.) in mice

	Group							
Component of behaviour	*I Intact animals*	*II Sham i.c.v. injection*	*III Intact animals*	*IV Saline i.c.v.*	*V Saline i.c.v.*	*VI NA (0.1 μg) plus DA 0.1 μg*	*VII Saline i.c.v.*	*VIII NA (1 μg) plus DA (1 μg)*
Walking (s)	299 ± 54	153 ± 32 *P* I/II <0.025	259 ± 46	130 ± 25 *P* III/IV <0.025	90 ± 12	110 ± 25 *P* V/VI >0.2	170 ± 17	50 ± 12 *P* VII/VIII <0.0005
Cleaning (s)	36 ± 10	53 ± 23 >0.25	30 ± 7	40 ± 11 >0.2	36 ± 8	0	60 ± 12	0 <0.0005
Sniffing (s)	40 ± 17	20 ± 9 >0.2	50 ± 18	20 ± 15 >0.1	20 ± 4	165 ± 20 <0.0005	20 ± 12	55 ± 9 <0.005
Immobility (s)	225 ± 59	374 ± 60 >0.1	261 ± 50	410 ± 40 <0.005	454 ± 42	326 ± 28 <0.0025	350 ± 19	495 ± 11 <0.0005
Number of rearings	14 ± 7	2 ± 1 <0.05	11 ± 4	2 ± 1 <0.05	2 ± 1	4 ± 1 >0.2	7 ± 0.8	2 ± 0.7 <0.0025

n = 20 (group I.IV), n = 10 (group V-III). Results expressed as a mean ± s.e.

Table 5 Behavioural effects of acetylcholine (ACh) in mice

	Group							
Component of behaviour	*I Saline (control)*	*II ACh (0.1 μg)*	*III Control*	*IV ACh (1 μg)*	*V Atropine (5 mg/kg) plus ACh (1 μg)*	*VI Control*	*VII ACh (10 μg)*	*VIII Atropine plus ACh (10 μg)*
Walking (s)	80 ± 12	62 ± 4 *P* I/II >0.1	114 ± 22	52 ± 15 *P* III/IV <0.0125	70 ± 12 *P* IV/V >0.15	116 ± 31	47 ± 7 *P* VI/VII <0.05	96 ± 13 *P* VII/VIII <0.005
Cleaning (s)	6 ± 4	14 ± 6 >0.1	10 ± 6	7 ± 5 >0.35	5 ± 2 >0.3	10 ± 5	10 ± 5 >0.9	10 ± 5 >0.9
Sniffing (s)	36 ± 4	50 ± 2 <0.01	52 ± 30	55 ± 30 >0.45	50 ± 25 >0.9	52 ± 11	7 ± 3 <0.0025	45 ± 5 <0.0005
Immobility (s)	480 ± 4	474 ± 15 >0.4	420 ± 30	485 ± 16 <0.05	475 ± 20 >0.9	420 ± 35	530 ± 23 <0.0025	449 ± 40 >0.1
Number of rearings	2 ± 0	2 ± 0 >0.9	3 ± 1	2 ± 1 >0.5	2 ± 1 >0.9	2 ± 1	0	2 ± 1

n = 10. Results expressed as a mean ± s.e.

Table 6 Behavioural effects of 5-hydroxytryptamine (5-HT) in mice

	Group				
	I	*II*	*III*	*IV*	*V*
Component of behaviour	*Saline (control)*	*5-HT (0.1 μg)*	*Control*	*5-HT (1 μg)*	*Methysergide (5 mg/kg) plus 5-HT (1 μg)*
Walking (s)	102 ± 21	72 ± 16 *P* I/II >0.1	86 ± 8	8 ± 2 *P* III/IV <0.0005	10 ± 5 *P* IV/V >0.3
Cleaning (s)	5 ± 3	15 ± 6 >0.05	3 ± 1	0 <0.01	0
Sniffing (s)	35 ± 7	30 ± 7 >0.35	41 ± 7	30 ± 7 >0.1	0
Immobility (s)	458 ± 23	498 ± 21 >0.1	470 ± 6	560 ± 8 <0.0005	590 ± 7 <0.01
Number of rearings	1 ± 0	1 ± 0 >0.9	3 ± 1	0 <0.01	0

n = 10. Results expressed as mean ± s.e.

obtained in animals already depressed by the experimental procedure has to be taken into consideration.

The behavioural effects of NA depend upon the dose. Low doses of NA increase, and higher doses decrease, locomotor activity. The behavioural effects of NA observed here in mice are very similar to those described in rats (Herman, 1970). These two dose-dependent central effects of NA are suppressed or even reversed by different adrenoceptor blocking agents. Andén & Strömbom (1974) concluded that phenoxybenzamine, but not phentolamine or propranolol, can be used to block selectively central and peripheral NA receptors in behavioural experiments. Our results indicating that phenoxybenzamine blocks the increased locomotor activity induced by low doses of NA are in agreement with this view. But in our experiments propranolol reversed the inhibition of locomotor and exploratory activities elicited by 1 μg of NA and suppressed the inhibition caused by 10 μg of NA. These facts suggest that behavioural depression caused by an excess of exogenous NA may be influenced by β-adrenoceptor blockade.

Dopamine also affects the behaviour of mice in a dose-dependent manner. It causes increased locomotor and exploratory activity in the lowest dose (0.1 μg), and an increase of locomotion and the appearance of tremors in a medium dose (1 μg). The highest dose used (10 μg) induced stereotyped behaviour. This last phenomenon and the observation that the behavioural effects of dopamine were blocked by pimozide, a drug which is considered to be a specific blocker of dopamine receptors in the brain (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970), suggest that the behavioural effects of exogenous dopamine applied intraventricularly are specific to dopamine receptors. Central dopamine action in mice resembles its effects in rats (Malec & Kleinrok, 1972). Simultaneous intraventricular injection of NA and dopamine in equal doses showed no synergistic or antagonistic effects in terms of the behavioural changes observed after the application of a single amine.

ACh decreased locomotor and exploratory activity in mice in a similar manner to that previously described (Herman *et al.*, 1972). These effects may be of muscarinic nature since they were abolished by atropine.

5-HT elicited depressant behavioural effects similar to those described in rats (Herman, 1973). However, methysergide considered as a 5-HT antagonist (McKeon Jr., 1967; Boakes, Bradley, Briggs & Dray, 1970) did not inhibit the behavioural phenomena evoked by 5-HT.

In conclusion it may be said that behavioural effects of catecholamines, ACh and 5-HT administered intraventricularly are similar to those described in rats by several authors. These effects, with the exception of 5-HT, can be blocked by antagonists of the amine investigated.

The author expresses his gratitude for a generous supply of substances, to Janssen (pimozide), ICI (propranolol), Smith, Kline & French (phenyoxybenzamine), Polfa (atropine) and Sandoz (Deseril). This work was supported financially by the Polish Academy of Sciences.

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(Received April 25, 1975.)