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Relative Role of Catecholamines in Head-Shaking of Infant Rats

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HOLMGREN, B., R. URBÁ-HOLMGREN AND M. VALDÉS. *Relative role of catecholamines in head-shaking of infant rats.* PHARMAC. BIOCHEM. BEHAV. 5(1) 29–34, 1976. – The relative contribution of catecholaminergic mechanisms in head-shaking (H-S) of infant rats was explored by comparing the H-S inducing effects of apomorphine and amphetamine in rats from 4–14 days old, and the blocking effect of neuroleptic drugs (chlorpromazine and haloperidol) and more specific α- and β-adrenergic receptor antagonists (phenoxybenzamine and propranolol), on amphetamine induced head-shaking. As apomorphine, but not amphetamine, may induce H-S in four-day-old rats, and the latter drug potentiates apomorphine induced H-S, even in days in which, if injected alone it has no effect, it is suggested that both dopaminergic and noradrenergic mechanisms are involved in H-S, thus differentiating this motor item from other motor patterns included in stereotyped behaviour. This suggestion is further supported by the demonstration that while D-amphetamine induced H-S is blocked by phenoxybenzamine, other stereotyped motor patterns continue unimpaired.

Catecholamines Amphetamine Head-shaking Apomorphine Infant rats Neuroleptics Stereotyped Behaviour Adrenergic blockers

IN a previous paper [23], devoted to the ontogeny of spontaneous and D-amphetamine induced head-shaking [H-S] in albino rats, we discussed the possibility that this rather simple normal motor item [30], which has been included by some authors [25, 26, 29] in stereotyped behaviour (SB) elicited by D-amphetamine, might be differentiated from other compulsive or perseverative motor patterns, like sniffing, gnawing, biting or licking, by its particular neurohumoral background. This hypothesis follows Norton's [30] suggestion that in the brain there might exist diffuse or anatomically localized command centers for items of behaviour, and Miller's [28] idea that different types of behaviour might be chemically coded.

As D-amphetamine has been proved to be able to release catecholamines from central and peripheral adrenergic synapses [13, 15, 16, 22], its behavioural effects may result from an activation of both dopaminergic and noradrenergic mechanisms. The persistance of D-amphetamine induced stereotypies after α-adrenergic receptor blockade with phenoxybenzamine [2], or dopamine-β-hydroxylase inhibition with either diethyldithiocarbamate [11, 19, 26, 33, 34] or FLA 63 [1] supports the conclusion that "dopamine, rather than norepinephrine is associated with the stereotyped behaviour induced by amphetamine" [13]. Selective stimulation of dopamine receptors with apomorphine, which is generally accepted as a dopaminergic agonist [9, 20, 31], also produces SB [9, 20, 21, 24, 25]. Stereotyped behaviour is blocked by neuroleptics [3, 6, 17]. It is also rather generally accepted that behavioural effects of catecholamines are probably balanced by other neurohumoral agents, especially by cholinergic mechanisms. In relation to stereotyped behaviour, Randrup and Munkvad [32] have referred to experiments showing that SB "is prolonged and enhanced by anticholinergics and weakly antagonized by cholinergics", and therefore conclude that "acetylcholine seems to have a certain inhibitory effect on stereotypy".

Several neuropharmacological effects thus exist, that may permit an experimental comparison of head-shaking and SB, and to judge if the former motor item is an integral part of stereotyped behaviour, or if it might be distinguished or dissociated from the latter. The present work concentrates on the analysis of the catecholaminergic contributions to head-shaking. The possible involvement of cholinergic mechanisms will be presented separately.

METHOD

The methods used in the present experiments were essentially the same as previously described in detail [23]. The experimental animals were infant albino rats, of a Wistar strain, born in the laboratory from pregnant females obtained from the Animal House of the Ministry of Public Health, Cuba. The results are based on 150 litters, each of which was reduced to eight rats 24–36 hr after birth. Animals were tested only once, in experiments always performed in morning hours (8–12 a.m.). Only animals with bodyweights within 1 SEM in either direction were used.

The only data that were quantified refer to head-shaking occurrence and total H-S time during the observation period of one hour. Each litter was equally distributed between the experimental and control groups.

The drugs used were the following: D-amphetamine, sul-

phate (Rhone-Poulenc); apomorphine, (Chimpharm); haloperidol (Richter); chlorpromazine; phenoxybenzamine, HCl (Smith, Kline and French); propranolol (I.C.I.), physostigmine (BDH Chemicals Ltd.).

Solutions were freshly prepared in saline (NaCl 0.9%) in dilutions such that the total volume to be injected intraperitoneally was equivalent to 0.01 ml/g bodyweight. Control animals were always injected with saline.

The statistical procedures are described with the results.

RESULTS

A. Experiments with Apomorphine

Infant rats from 3–14 days in age were injected with a standard dose of apomorphine (5 mg/kg), and the occurrence of H-S and its total duration were recorded. As may be observed in Table 1, apomorphine increases both occurrence and total duration of this motor item at all ages examined, from 4–14 days. All differences with the controls are statistically significant, with the only exception of H-S occurrence at 9 days. If the results in Table 1 are compared with those previously published on D-amphetamine elicited H-S [23], some important differences seem noteworthy (see Discussion and Fig. 5). The range of ages in which apomorphine increases or induces H-S is wider, occurrence of this motor item is higher, but total duration is lower. On the other hand, locomotor activity after apomorphine is quite moderate, if compared with the intense effect exerted by D-amphetamine.

B. Interaction Between Apomorphine and D-amphetamine Effects

On the account of the observations mentioned in the preceding paragraph, it seemed interesting to explore if synergic effects on H-S could be obtained by the administration of both drugs.

If infant rats which had been injected with apomorphine (5 mg/kg) received, one hour later, an additional injection of D-amphetamine (5 mg/kg), the initial effect of apomorphine was strengthened, even in those postnatal days in which amphetamine per se has no H-S eliciting effect, i.e., at the 4th and 12th postnatal days (Fig. 1). This synergic or potentiating effect is particularly dramatic at the 4th postnatal day, in which total duration of H-S shows a ten-fold increase. Head-shaking occurrence also changes as a result of this combination of both drugs: at the 4th postnatal day it rises from 10–57%; at 9 days from 61–72%, but at the 12th day it is reduced from 40 25%, as if in some cases increased locomotion or stereotypies induced by D-amphetamine exerted an inhibitory effect on H-S. A similar effect is obtained when both drugs are injected simultaneously, but, when the order of administration is reversed, that is, amphetamine being injected one hour before apomorphine, the synergism is not observed (Fig. 2). This experiment was done only in rats 4 days old.

C. Experiments with Catecholamine Blockers

The experimental design was the following. Only rats 9 days old were used, because of the higher incidence and longer H-S times observed at this age [23]. The animals were observed during 15 min after the injection of a mixture of D-amphetamine (5 mg/kg) and physostigmine (0.1 mg/kg), for an initial quantification of the head-shaking effect. Physostigmine was added because in preliminary experiments (Holmgren and Urbá-Holmgren, unpublished results) we have observed that this drug increases H-S occurrence and total head-shaking time. Only rats with intense head-shaking were selected for comparison of the effects exerted by a second injection of haloperidol (0.5 mg/kg), chlorpromazine (1 mg/kg), propranolol (5 mg/kg), phenoxybenzamine (2 mg/kg), or saline.

In Fig. 3 the effect of the two former neuroleptic drugs

TABLE 1

COMPARISON OF SPONTANEOUS AND APOMORPHINE INDUCED HEAD-SHAKING IN INFANT RATS

Age (days)	Spontaneous N	Spontaneous Occurrence %	Spontaneous Total Mean H-S Time (sec)	Apomorphine N	Apomorphine Occurrence %	Apomorphine Total Mean H-S Time (sec)
3	26	0	0	26	0	0
4	40	0	0	40	8.1	8.2
5	40	0	0	37	12.5	17.0
6	30	6.7	1.4	30	34.4	72.8
7	32	9.4	3.7	30	61.3	23.2
8	32	12.5	6.2	30	61.3	35.5
9	44	45.5	27.8	30	61.8	41.7
10	36	13.9	3.1	30	46.9	34.3
11	30	6.7	1.7	26	41.6	16.8
12	56	5.4	0.5	30	40.6	19.4
13	40	0	0	24	18.2	4.9
14	20	0	0	24	8.3	2.4

Statistical significance (Chi² Test) for H-S occurrence differences between apomorphine injected and saline injected rats: $p<0.01$ for all ages between 4 and 14 days, with the exception of 9 days, in which the differences are not significant. For the Total Mean H-S Time, the differences between both groups, including nonshaking animals, are significant at the level of $p<0.01$ from 4–12 days (one-tail Mann-Whitney U Test).

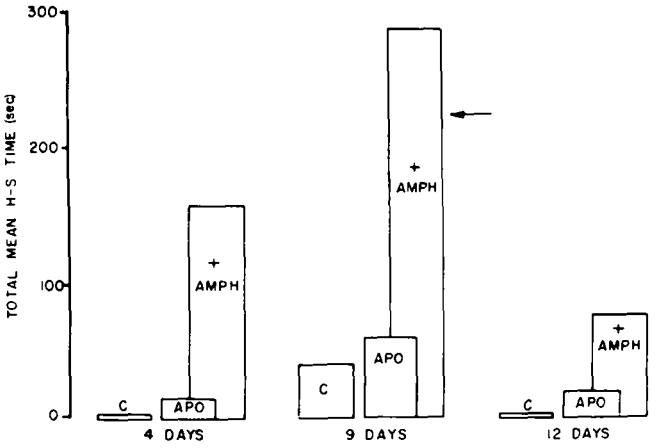

FIG. 1. Amphetamine effect on H-S of rats pre-injected with apomorphine (5 mg/kg). APO, apomorphine (5 mg/kg). + AMPH, same animals as above, which received amphetamine (5 mg/kg) one hour later. C, control animals injected with saline. Each column represents Total Mean H-S for 20 animals. Statistical significance (one-tail Mann-Whitney U Test) between the H-S times after apomorphine, and after the additional injection of amphetamine: 4 days, $p<0.003$; 9 days, $p<0.02$; 12 days, $p<0.03$. ← Arrow indicates total mean H-S time when only D-amphetamine is injected [23].

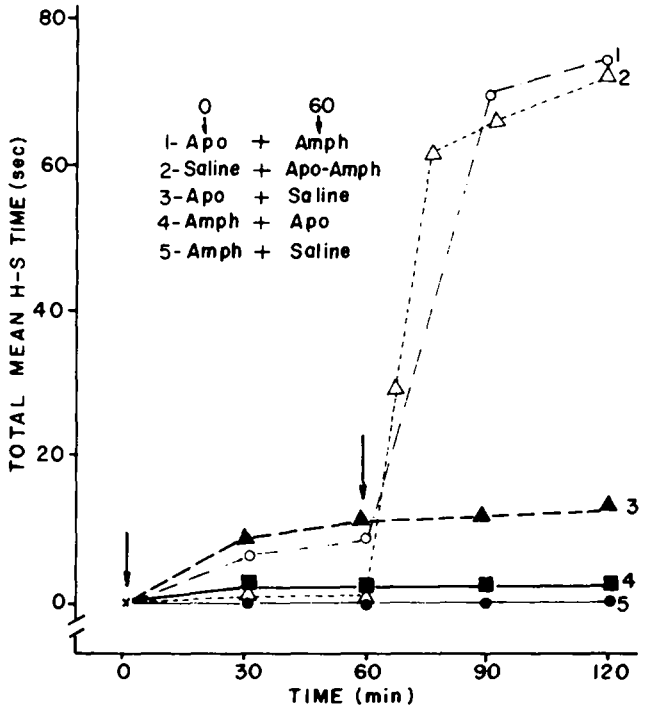

FIG. 2. Interactions of apomorphine and amphetamine on H-S of 4-day-old rats. Influence of the order of administration of both drugs. Arrows indicate the moment of injection. Five mg/kg was used in both cases. N for each group = 15. Statistical significance in total mean H-S time at 120 min between: 1 vs 4, $p<0.001$; 1 vs 3, $p<0.001$; 1 vs 2, NS; 2 vs 3, $p<0.001$ (one-tail Mann-Whitney U Test).

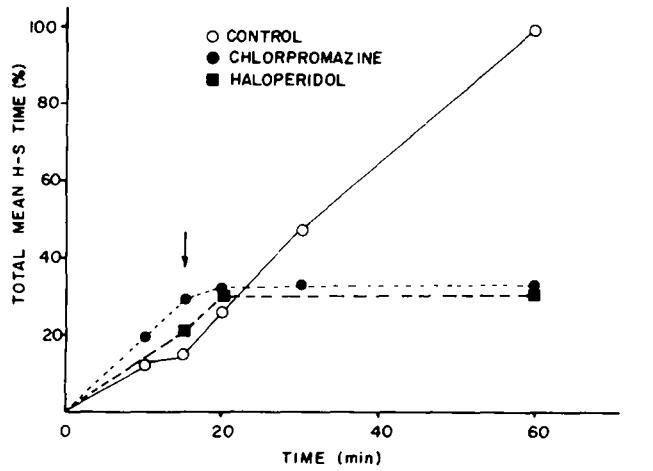

FIG. 3. Effect of neuroleptics on D-amphetamine induced H-S. The arrow indicates the moment in which chlorpromazine, haloperidol or saline were injected to rats that had received D-amphetamine at 0 time. The reduction in total mean H-S time observed in the neuroleptic injected rats is significant at the level of $p<0.001$ (one-tail Mann-Whitney U Test). N for different groups: haloperidol, 20; controls, 19; chlorpromazine, 13; controls, 13.

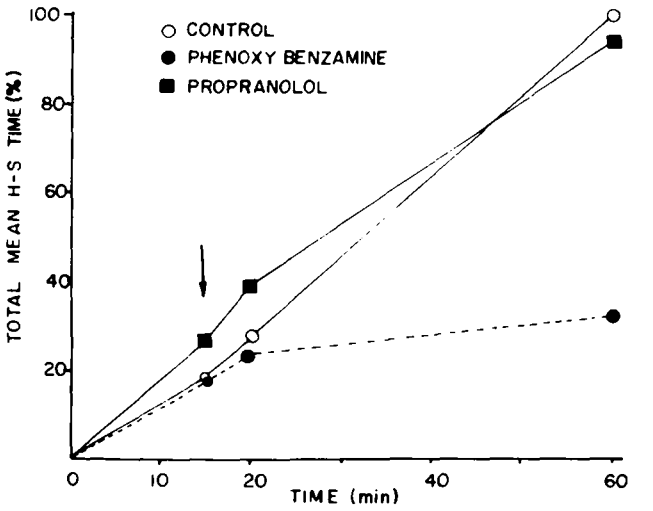

FIG. 4. Effects of phenoxybenzamine and propranolol on D-amphetamine induced H-S. Amphetamine (5 mg/kg) injected at 0 time. The arrow indicates the moment at which the blocking agents were injected. Statistical differences (Mann-Whitney U Test): Control vs Phenoxybenzamine, $p<0.001$; Control vs Propranolol, NS. Number of animals: Phenoxybenzamine, 16; controls, 10; Propranolol, 15; controls, 13.

on H-S is illustrated. Both drugs suppress head-shaking within 5 min in all animals, while the additional injection of saline does not produce any disruption in the course of H-S.

The effects of the more specific α- and β-adrenergic receptor blocking agents, phenoxybenzamine and propranolol, respectively, are shown in Fig. 4. At the dose used, phenoxybenzamine reduces H-S in all animals, but in only 50% of them a complete suppression is obtained. The others continue showing sparse and brief H-S episodes. It should be pointed out that suppression of H-S after phenoxybenzamine contrasts with the persistence of intense stereotyped sniffing and/or licking, even at so high

TABLE 2

AMPHETAMINE INDUCED H-S IN INFANT RATS PREINJECTED WITH PROPRANOLOL

Groups	N	Total Mean H-S Time (seconds) 0–30 min	30–90 min
Control	16	1	191
Propranolol	16	2	246

Experiment done in 9-day-old rats which had been injected at 0 time with propranolol (5 mg/kg), or saline (controls), and received, 30 min later, D-amphetamine (5 mg/kg). Differences are not significant (Mann-Whitney U Test).

doses of phenoxybenzamine as 20 mg/kg, tried during preliminary experiments.

As may be observed in Fig. 4 propranolol appears not to exert any effect. As this could be due to a longer latency in its action, an additional experiment was done, in which the β-adrenergic blocking agent was injected 30 min before D-amphetamine. Even with this experimental design, propranolol did not produce any effect on head-shaking (Table 2).

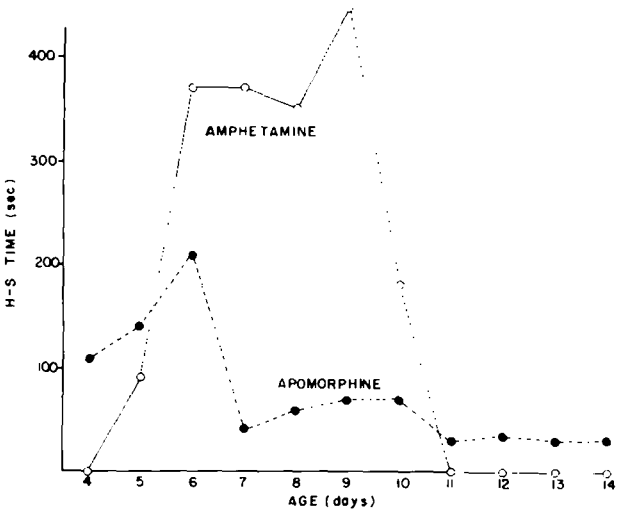

FIG. 5. Comparison in H-S inducing effects of apomorphine and D-amphetamine, when nonshaking animals are excluded. D-amphetamine data taken from Holmgren *et al.* [23]. Statistical significant differences (Mann-Whitney U Test): 5–6 days, NS; 7 days, $p<0.001$; 8 days, $p<0.001$; 9 days, $p<0.003$; 10 days, NS. Results at 4 and 11–14 days could not be compared because no animals injected with D-amphetamine presented H-S at these ages.

DISCUSSION

Confirming experimental results of several experiments [9, 20, 21, 24, 25] we have observed that apomorphine induces stereotyped behaviour, which is rudimentary in the very early postnatal days, but is very well developed by the 9th or 10th day. The action of apomorphine differs from the one observed after D-amphetamine in its relatively moderate locomotory effect.

The fact that apomorphine is capable of eliciting H-S in 4-day-old rats, suggests that this motor item is evokable by dopamine sensitive mechanisms, the receptors being able to react with apomorphine even before functional maturation of the presynaptic structures which, according to the results with amphetamine, proceeds from the 5th day onwards [23]. If the quantitative data on apomorphine induced H-S are compared with the previously published results with D-amphetamine [23], H-S occurrence appears higher under apomorphine. But if the strength of the effect is judged by its total duration during the observation period, D-amphetamine would appear to exert a stronger effect. This is especially illustrated in Fig. 5, in which average H-S duration after apomorphine and D-amphetamine are compared, excluding non-shaking animals.

The synergic or potentiating effect observed when D-amphetamine is injected after apomorphine (Experiment B), together with the differences in age, range and strength of the effect observed when these drugs are injected separately, strongly suggest that different neuron systems are activated by these drugs, apomorphine probably stimulating only dopamine-sensitive receptors [9, 20, 25] and D-amphetamine acting on both dopaminergic pathways and noradrenergic mechanisms [13, 15, 22, 32], the latter contributing vigourously to head-shaking intensity. A relatively analogous interpretation has been offered to explain the differences in the effect of these two drugs in the reversal of tetrabenzaine suppression of schedule-controlled behaviour [11].

The experiments with neuroleptics, even if not conclusive because of insufficient specificty of their action, support the general idea that both DA and NA mechanisms are involved in head-shaking. Chlorpromazine, which blocks both dopamine and α-adrenergic receptors [6,12] suppresses H-S totally at the dose we have used. Haloperidol, which at low doses seems to have a stronger effect than chlorpromazine on dopamine receptors [4] also blocks H-S completely. It may be recalled that these two drugs abolish both locomotor and stereotyped behaviour induced by D-amphetamine or apomorphine [3, 6, 17].

The results with phenoxybenzamine perhaps contribute more to a pharmacological dissection of H-S in regard to its neurohumoral basis. While stereotyped movements are unaltered by the drug, thus confirming previous observations of Andén [5], both spontaneous and D-amphetamine induced H-S is reduced or abolished by this α-adrenergic blocking drug. Without excluding the possibility that part of this antagonistic action might be exerted on dopamine-sensitive receptors [27], it seems to us more probable that the blocking effect takes place on α-adrenergic receptors, because of the persistence, under phenoxybenzamine, of stereotyped movements, the dopaminergic background of which seems quite well documented [9, 20, 26, 33, 34]. Nevertheless, an alternative and apparently coherent interpretation of the different effects of phenoxybenzamine on head-shaking and stereotyped behaviour can be built on the basis of York's results with micro-ionophoretically applied dopamine on putamen cells [37]. In these experiments 31% of putamen cells were depressed by dopamine, and 44% were excited, and it appeared that α-adrenergic blockers were generally more effective antagonists of dopamine excitation than β-blockers. On the contrary, only β-adrenergic blocking drugs showed any degree of antagonism to dopamine-induced depressions. If it is assumed that head-shaking might be initiated by excitation of putamen or pallidal cells, a blocking effect of phenoxybenzamine at this level may

curtail the development of head-shaking without affecting dopamine-inhibitory effects. The lack of any effect on H-S shown by our experiments with propranolol also fits in this hypothetical explanation.

We have formerly [23] made an effort to explain head-shaking in infant rats as the consequence of an early period of instability, with oscillatory tendencies of the stretch reflex systems of the head and neck muscles, without discarding an eventual supraspinal pacemaker. We have also suggested that the descending noradrenergic bulbospinal fibres [14,18] might be an important link in the pathways responsible for head-shaking. As very deep changes in reflex function and synaptic transmission have been observed in spinal animals treated with DOPA [7, 8, 10, 34, 35], or with amphetamine [35,36], effects which are rapidly reversed with phenoxybenzamine [7,8], it is tempting to implicate these descending pathways in an explanation of head-shaking. The intense effect of D-amphetamine at the spinal level [35,36] while apomorphine has none [2] might contribute to the differences in strength of the H-S inducing effect of these two drugs.

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