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Spontaneous and Amphetamine Induced Head-Shaking in Infant Rats

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HOLMGREN, B., R. URBÁ-HOLMGREN AND M. VALDÉS. *Spontaneous and amphetamine induced head-shaking in infant rats.* PHARMAC. BIOCHEM. BEHAV. 5(1) 23–28, 1976.– A variable proportion of albino rats 6–11 days old exhibit spontaneous and infrequent rotatory head-shaking episodes. This motor pattern is slightly anticipated and significantly increased in occurrence and duration by the administration of D-amphetamine (5 mg/Kg), with a maximal effect of the drug on the 9th day. The rate of amphetamine induced rhythmic head oscillations increases with age from below 5 cps on the 5th day to about 9 cps on the 10th day. The results are discussed in relation to maturation of both the underlying catecholaminergic pathways, activated by D-amphetamine, and the stretch reflex systems of the head and neck muscles participating in the rhythmic activity. Emphasis is placed on the difference between head-shaking and stereotyped activity.

Neural maturation Amphetamine Catecholamines Head-shaking Rhythmic activity Stereotyped behaviour

IN ORDER to develop a simple test to follow the functional maturation of the dopaminergic pathways in the central nervous system, during the early postnatal period of the rat, we have been trying to quantify stereotyped activity induced by amphetamine and apomorphine. Such stereotyped behaviour has been studied by several research groups [1, 5, 22, 23] and has been correlated with the activation of dopaminergic synapses in the corpus striatum [1,6]. Its ontogeny in the rat has been described recently [11].

In preliminary experiments we were able to confirm the observations of the aforementioned authors, and the rudimentary stereotyped sniffing, tongue protrusion or licking, and gnawing or gumming behavior, characteristic of infant rats injected with amphetamine or apomorphine, and the locomotor bursts induced by the former drug. But we have paid greater attention to relatively frequent episodes of head-shaking, in which a clear rotatory component around the sagittal axis could be recognized, motor item scantly mentioned in the literature as part of stereotyped behaviour [11,18] or as a normal behavioural item in the rat [19]. As head-shaking is easily detected by simple observation, and measurable in frequency and duration, we decided to make a quantitative description of this motor pattern and to study its ontogenetic development, with the hope that on its basis a maturational index might be devised.

METHOD

The observations and experiments to be described were done in albino rats, orginally of a Wistar strain, obtained from the Animal House of the Ministry of Public Health, Cuba. Pregnant females were maintained in the laboratory for a couple of days before parturition, the moment of which was estimated with an approximation of ± 8 hours. Litters were reduced to 8 animals between 24 and 36 hr after birth. Their weights were controlled regularly until the experimental day (Fig. 1). The final results are based on animals only within 1 SDM of the mean weight in either direction. After the preliminary experiments our observations were restricted to animals from 4–15 days after birth. The general results are based on 140 litters, which were tested only once. The dose-effect curve for amphetamine induced head-shaking is based on 20 litters, tested on the 9th postnatal day. Head-shaking rate was recorded in a total of 77 rats, from 5–10 days old.

D-amphetamine sulphate was dissolved in saline (0.9% NaCl) so that the total volume to be injected was equivalent to 0.01 ml/g weight. Controls were injected with saline.

The experiments were performed in the morning (8–12 a.m.). After being injected, 2–4 rats were placed together in observation boxes (25 x 40 x 10 cm) with vinyl plastic covered floor. The animals were observed during one hour, noting spontaneous activity, immobility or locomotion, noteworthy postural attitudes or stereotyped behaviour. The only motor acts to be quantified were rotatory head-shaking episodes, the moment and duration of which were recorded with stopwatches. Small vertical or horizontal intentional or rest tremor of the head, or slow lateral, as if exploratory head movements were not recorded. The oscillatory frequency of head-shaking was measured with a photoresistor, placed at the bottom of a slot 10 x 3 x 3 cm, excavated in thick polyesterene foam. The changes in illumination on the photoresistor's window, due to the shaking head of the rat placed in the slot, unbalanced a Wheatstone bridge, and were recorded on a two-channel polygraph. Statistical procedures will mentioned with the Results.

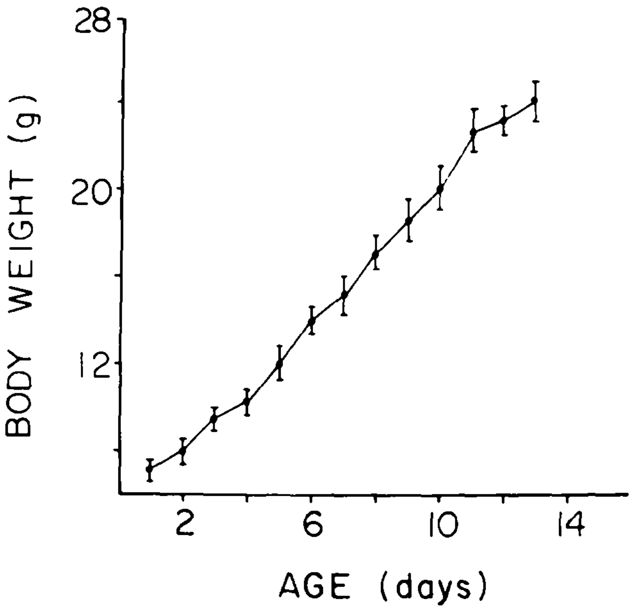

FIG. 1. Body weight as a function of age. Values are expressed as Mean ± SDM. The curve is based on a variable number of animals: minimum, 54 at 10 days; maximum, 130 at 1 day. Only animals within 1 SDM in either direction were used.

RESULTS

Spontaneous Activity

Normal infant rats, during their first 5 days of age, separated from their mothers, and placed in an open field, either alone or in small groups, exhibit a very restricted spontaneous motor repertoire. During an observation period of one hour they remain passive, quiescent or asleep most of the time. On the 4th or 5th day, crawling with the forelimbs and lateral movements of the head and trunk permit them to circle incompletely, pivoting at the hindlimbs. Some slow lateral searching movements of the head may also be observed. From the 6th day onwards the rats are much more active, especially during the first minutes, the degree of activity apparently depending on the intensity of previous handling. Mobility expands rapidly in the following days. The animals perform forward and backwards locomotory movements, and seem to explore their surroundings with their vibrissae and by sniffing behaviour. Occasionally scratching and rudimentary grooming reflexes, or awkward simultaneous sweeping movements of both forepaws over the ears are observed. When in groups they may push each other as if searching for contact or suckling possibilities, and tend to huddle, especially in the corners of the observation boxes. Head-lifting movements are apparent by the 6th day, and with support on the corner walls, the rats 6–7 days old may manage to stand on the hindlimbs and perform alternating movements of the forelimbs.

The injection of a standard dose of amphetamine (5 mg/kg) produces an intense increase in spontaneous activity at all ages examined, and displaces the appearance of the total motor repertoire to the earlier days. Several motor items which normally appear at the 6th and 7th day are evoked already at the 3rd or 4th day. Rudimentary stereotyped activity, intermittent licking and sniffing during reverse locomotion is also seen, being quite intense by the 10th day and later.

Head Tremor and Head-Shaking

When infant rats move their heads while sniffing or exploring, very fine vertical or horizontal tremor is frequently observed. Occasionally, during rest periods, regular head-rocking or head-shaking movements appear, with a predominant rotatory component around the sagittal axis, especially when the chin remains supported on the floor or on another animal. Lateral oscillatory components may be observable when the animal lifts its shaking head, but this is quite unusual.

In some animals, especially those that exhibit head-shaking before being injected, this motor pattern increases immediately after amphetamine administration. But, in general, head-shaking tends to be more notorious after the first 10–15 min, when the increase in overall activity induced by the drug has receded. This points to head-shaking as a motor pattern of resting animals. When observed in groups, the mutual interference due to moving animals frequently interrupts head-shaking episodes. It is not clear if this motor item might be present in sleeping animals, because in infant rats, with eyes not yet open, it is difficult by simple inspection to judge if a quiescent animal is asleep. Nevertheless, on many occasions, when animals which had shown head-shaking, but had remained motionless and perhaps asleep for rather long periods, were grasped and placed on their backs as if to evoke righting reflexes, after recovering their normal resting posture, they began quite often with rocking head movements.

Quantitative Aspects of Head-shaking (H-S)

(a) H-S occurrence. Spontaneous or D-amphetamine induced head-shaking is not a universal trait. It is evident only in a fraction of the infant rat population, fraction which changes with age, and has its maximum at 9 days (Fig. 2). As may be observed in this figure, D-amphetamine increases the percentage of H-S animals from 5–9 days, the effect being statistically significant (Chi^2 Test) only from 5–8 days. While no H-S was observable in control animals of 5 days, it has been observed in several animals of this age after D-amphetamine. On the contrary, while a 12.5% of 11 days old control rats exhibited H-S, it did not appear at this age after D-amphetamine administration.

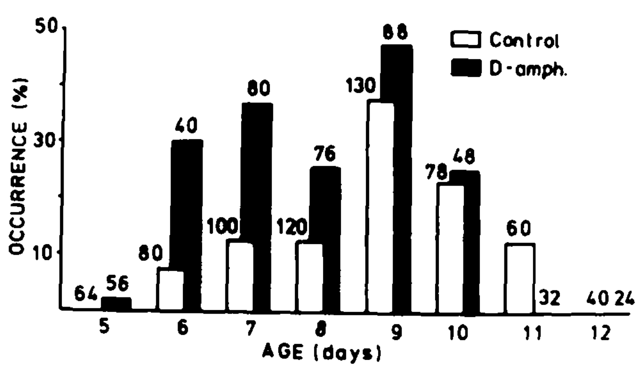

FIG. 2. Head-shaking occurrence in infant rats. The increases induced by D-amphetamine are statistically significant (Chi square test) at the level of $p<0.001$ for 5–7 days, and $p<0.01$ for 8 days. Number of animals indicated in each vertical bar. Other details in the text.

As rats in this series of experiments were observed only once, it is possible that the high percentage of non-shaking animals might be due to the tests being performed at a day in which this motor item had not yet appeared or had already disappeared. To disclose this possibility, 4 control litters were observed daily during one hour, from 6–11 days. The percentage of head-shaking animals had its peak at 8–9 days, but some cases existed with H-S at the 7th or 10th day, not responding at the 8th or 9th. H-S occurrence, if considered for the whole period (6–11 days) in these 32 rats, reached 87.5%. The above mentioned observations seem to be valid also for D-amphetamine evoked H-S (see experiment described under (*e*) and the one illustrated in Fig. 6).

(b) Duration of H-S episodes. Head-shaking episodes are relatively brief, not longer than 66 sec in control animals, their duration not being related to age or sex. D-amphetamine induces a marked increase in duration, up to a maximum of 458 sec, particularly in the earlier days (Fig. 3).

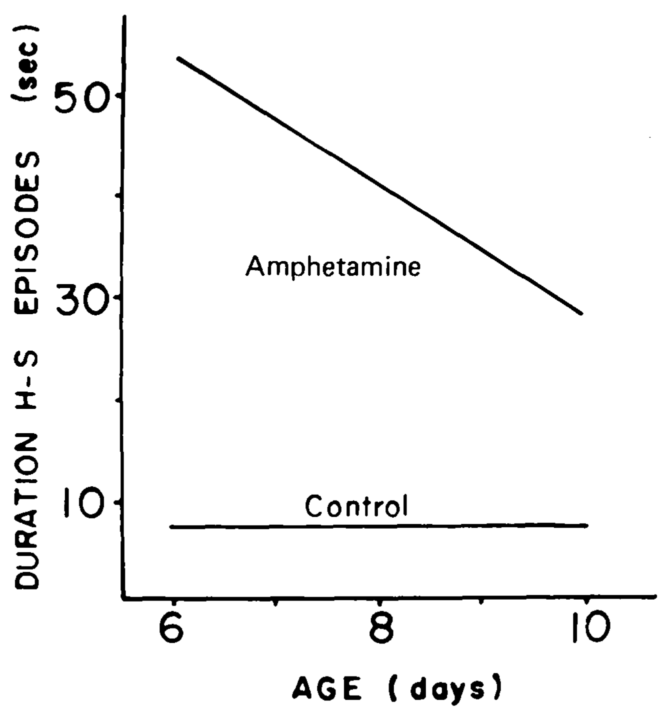

FIG. 3. Linear regression indicating proportionality between the duration of amphetamine induced H-S episodes and age. It is based on the following numbers of H-S episodes: 6 days, n = 75; 7 days, n = 250; 8 days, n = 190; 9 days, n = 300 and 10 days, n = 110.

(c) Total mean H-S time. In Fig. 4 the total mean H-S time in one hour observation periods is plotted against age, both for control and D-amphetamine injected rats (non-shaking animals also included for the average calculations). The H-S time for 9 days in control rats is significantly different from all other ages of the control group as inferred from Kruskal-Wallis Tests performed for all ages (6, 7, 8, 9, 10; $p<0.001$) and excluding 9 days (6, 7, 8, 10; $p>0.01$). Differences between control and amphetamine injected animals are statistically significant for all ages from 6–10 days (one tail Mann-Whitney U Test, see Fig. 4). A Kruskal-Wallis Test for H-S time data among animals from 6–10 days in the amphetamine injected group points to heterogeneity in the population ($p<0.01$) but the only statistically significant difference in H-S time between ages in the 6–10 days range for the amphetamine injected rats is for 9 vs 10 days groups, when examined with the one tail Mann-Whitney U Test ($p<0.001$).

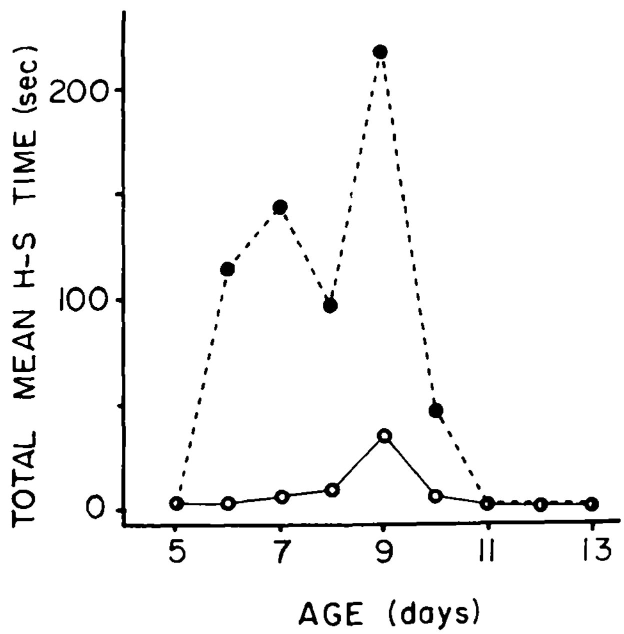

FIG. 4. Total Mean H-S time. Differences between controls, o——o, and D-amphetamine (5 mg/Kg) injected rats, •– – –•, are statistically significant with the one tail Mann-Whitney U Test at the levels indicated: 6–7 days, $p<0.01$; 8 days, $p<0.02$; 9 days, $p<0.001$; 10 days, $p<0.05$. Number of animals as in Fig. 2. Other details in the text.

(d) Dose-response curve for amphetamine induced H-S. In order to ascertain if the dose of D-amphetamine we have used to explore H-S was adequate for this purpose, different doses between 0.5 and 20 mg/Kg were tried on 9 days old rats. The resulting dose-response curve, plotted on semilogarithmic scale is shown in Fig. 5. From 2–20 mg/Kg the H-S times are not significantly different (Kruskal-Wallis Test), but a suggestive peak seems to appear at 15 mg/Kg.

(e) Head-shaking oscillatory rate. As by simple visual observation it appeared that H-S was faster as age increased from 5–10 days, recording of H-S with a photoresistor device was performed in some litters. A clear demonstration of this change in H-S frequency is illustrated in Fig. 6. It corresponds to a litter of 8 rats that were injected on three occasions with D-amphetamine (5 mg/Kg) at the ages of 5, 7 and 9 days. Five, four and five animals responded at the indicated experimental days. A neat linear relation between average H-S rate and age is evident for this group. When plotting the data for all 77 animals examined on different days, results stand out as shown in Fig. 7. From these experiments the impression is also gained that repeated injections of D-amphetamine on alternate days contribute towards an increase in the number of animals responding, and in the facility to record H-S with a procedure that implies an amount of handling which usually interrupts the head-shaking episodes.

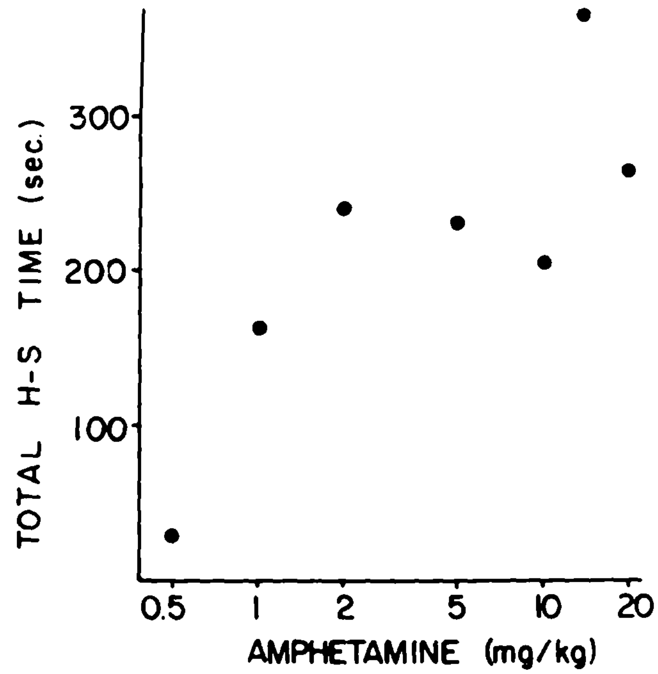

FIG. 5. Dose-response curve for D-amphetamine induced H-S. Each point represents Total Mean H-S time for 16 rats, 9 days old. Values for 0.5 and 1 mg/kg are significantly different from those with higher doses (Kruskal-Wallis Test, $p<0.01$). From 2–20 mg/kg the values do not differ significantly.

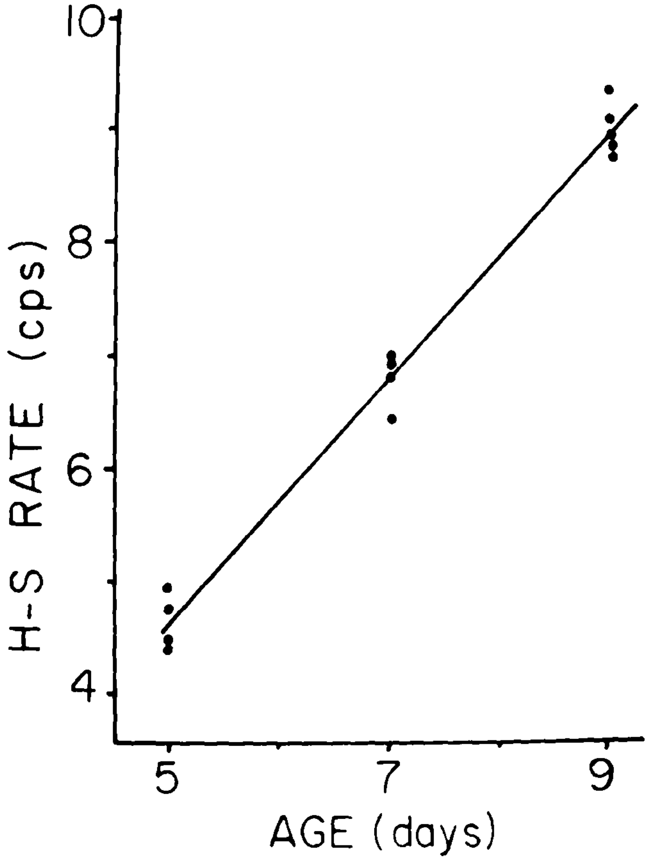

FIG. 6. H-S rate as a function of age. Data obtained from a litter injected with D-amphetamine on three alternate days. Line passes through mean values.

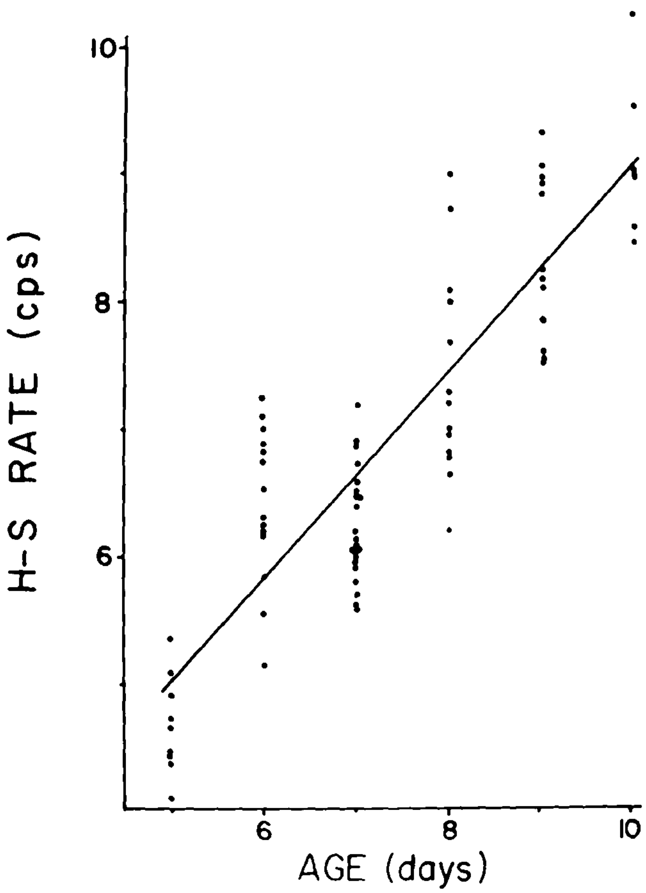

FIG. 7. Head-shaking rate versus age. Linear regression for data obtained from 77 animals. R = 0.8682, ($p<0.001$).

DISCUSSION

We have focussed our attention on a very simple motor pattern: head-shaking in infant albino rats. It appears in about 40% of the population of the line of rats studied, and is more evident during a short lapse of time, from 6–11 days of the postnatal period. The total time in which infant rats are engaged in H-S is generally less than a minute in one hour of observation. Our results show that this motor item may be elicited or significantly increased by D-amphetamine; after drug administration it appears in a higher proportion of the population, lasts longer, and the postnatal period during which it appears is slightly anticipated.

Several points seem worthwhile discussing. Is head-shaking a normal pattern of activity that may become stereotyped under amphetamine? Or, is it a rather dis-kynetic phenomenon, a sort of tremor or clonus due to a supraspinal imposed rhythm, or to facilitation or release of an inherent rhythmicity of the reflex arcs controlling neck muscles? By what mechanism does amphetamine induce or facilitate this behaviour? Why does it appear during a so particularly limited postnatal period, and not in every rat?

Head-shaking in normal adult rats seems to be a motor pattern of very secondary importance, or so inconspicuous as to escape attention or deserve but a very scant mention in the literature describing motor behaviour [19]. It may be understood as a reflex or purposive movement, useful, for instance, to drive away insects from the animal's head. If performed continuously, without apparent aim, while other forms of behaviour are absent, it may enter into the category of stereotyped, perseverative or compulsive movements which have been observed in different animals after the injection of amphetamine, apomorphine or other stimulant drugs [21,22].

In rodents, sniffing, tongue protrusion or licking, biting or gnawing appear as the predominant stereotyped behaviour. But "very rapid and persistent head movements" have been included in rat stereotypy by Naylor and Olley [18]. Slower lateral movements of the head and eyes, from side to side, as part of a visual stereotyped searching behaviour are described for the cat and monkeys [22]. Similar head movements were recently observed in cattle after intravenous injections of apomorphine [26]. Rhythmic rocking of the head also appears in infant humans, infant chimpanzees and infant monkeys, when put to bed or when lonely and unhappy, and has been interpreted as a comfort habit [20].

Rotatory head-rocking or head-shaking in infant rats, with closed eyelids, seems not to be a convincing expression of stereotyped searching behaviour. Another way to look at this motor pattern is to consider it as a head clonus, or a reciprocally coordinated head tremor, falling thus in line with other examples of increased rhythmic activities: aimless locomotory spurts, or alternating movements of the forelimbs while rearing, which are also observed in rats under amphetamine.

That these motor effects do not appear before the 5th postnatal day may be correlated with the relative functional immaturity of the monoaminergic pathways. Tyrosine-hydroxylase levels in the striatum of the rat increase in about 140% from 4–16 days [17]. Turnover of striatal dopamine, as estimated by the homovanillic acid/dopamine ratio, reaches a maximum around the 12th postnatal day [10]. Later on, feedback regulatory mechanisms would contribute to a decrease in catecholamine turnover.

As the neuropharmacological effects of amphetamine are explained by the drug being capable of releasing central dopamine, and central and peripheral norepinephrine [2], one or the other, or both neurotransmitters might be held responsible for the head-shaking elicited by D-amphetamine in infant rats. If head shaking were only an aspect of stereotyped behaviour, dopamine would presumably be more involved; norepinephrine, if head-shaking were more a manifestation of hypermotility. It may be recalled that stereotypy and hypermotility seem to have dopamine and norepinephrine as their respective major underlying neurohumoral factors [24,25].

As the only catecholaminergic pathways descending to the spinal cord are noradrenergic [4], it seems natural to look for an explanation of head-shaking involving norepinephrine. Some experiments by Viala and Buser [28] may offer a hint in this direction. These authors showed that in decerebrate, curarized and anesthetized rabbits, simultaneous locomotive rhythmic electrical activity could be detected in motor nerves of both hindlimbs. This rhythmic activity disappeared with spinal section. If D-amphetamine or L-DOPA was injected, rhythmic activity reappeared, but the simultaneous bilateral pattern was replaced by alternating activity in motor nerves from one and the other hindlimb. A tendency towards rhythmic activity through longlasting reciprocal activation of flexor and extensor alpha motoneurones in acute spinal cats after L-DOPA may also be deduced from the review by Lundberg [16].

In a separate paper, neuropharmacological evidence will be presented which points to both dopamine and norepinephrine contributing to head-shaking in infant rats, and to cholinergic mechanisms being also involved. This apparently simple motor pattern would thus have a multifactorial neurohumoral background, differing from stereotyped behaviour in the relative contribution of these neurohumoral factors (Holmgren and Urbá-Holmgren, in preparation).

Recalling that both the afferent link of the stretch reflexes and gamma efferent innervation of muscle spindles mature postnatally in the kitten [27], and assuming that stretch reflex maturation is also a postnatal process in the rat, an early period of instability, with marked tendency towards oscillation of the stretch reflex system of the head and neck muscles would be understandable. Following Glaser and Higgins' line of thought [8], the early lack of cerebellar support to gamma efferent tonus might also be a contributing factor, as it is well known that cerebellar development in the rat lags behind the rest of the brain's development [29].

The gradual increase in head-shaking rate, from approximately 5–10 cps, that takes place from 5–10 days, would be an objective expression of the maturation of the stretch reflex system, with several hypothetical intervening factors: increase in conduction velocity in peripheral nerves and in speed of contraction of the maturing neck muscles, earlier response of muscle spindles in the stretched muscles, shorter central reflex latencies, etc. [27]. The shortening of H-S episodes under amphetamine with increasing age (Fig. 3) also suggests that some stabilizing influences are gradually developing. The disappearance of head-shaking after the 10th or 11th postnatal day would mean that around these days the stretch reflex system of head-rotating muscles reaches stability. But evidently, the possibility that H-S results from rhythmical activity of a supraspinal pacemaker, i.e. at the nucleus insterstitialis of Cajal in the subthalamic region, which according to Hess coordinates rotation of the head around the sagittal axis [9], at the pallidum, or at a lower level, involving the olivary-cerebellar-reticular/vestibular-spinal loops, as in the 8–12 cps harmaline induced tremor [12, 13, 14, 15], cannot be discarded a priori.

A final but important problem must be considered. In the line of rats used in our experiments only about 40% of infant rats injected with D-amphetamine on the 9th postnatal day exhibited H-S. But if one estimated H-S occurrence from experiments in which the same litters were observed or injected on several occasions, this rather low percentage increased up to 87.5%. As in litters tested only once, about 12% of them showed no H-S subjects, and a similar proportion of litters were all head-shakers, all the intermediate possibilities also existing, these observations suggest that genetic factors may be involved in the distribution of H-S in the population. Testing for amphetamine induced H-S in a different line of rats, we have obtained 58% of H-S animals at the 9th postnatal day. It would be interesting to explore if infant rats of other strains might be more homogeneous in regard to the occurrence of this motor pattern, thus favouring its standardization and use as a maturational test.

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