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Stereotyped Activities Produced by Amphetamine in Several Animal Species and Man*

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The word "stereotype," in the present and previous papers on amphetamine (Randrup and Munkvad, 1963, 1965, 1966; Munkvad and Randrup, 1966), is used to describe a form of behaviour with little variation. In extreme cases one single activity is performed continously and dominates the animal's behaviour, e.g. sniffing at the cage wires. In less pronounced cases the animals repeat certain behavioural repertoires many times in a regular fashion as described in the examples below. (See also Lát and Gollova, 1964.)

The term "stereotype" is also used by others as a description of abnormal behaviour after amphetamine (Lát, 1965; Hauschild, 1939; van Nueten, 1962; Lapin and Schelkunov, 1965; Quinton and Halliwell, 1963; Chance and Silverman, 1964), but this behaviour is also characterized as compulsive ("Zwangsnagen," Janssen *et al.*, 1965) or purposeless ("constant purposeless searching head movement," Emele *et al.*, 1961).

We prefer the term "stereotype" because it is exclusively descriptive. Stereotyped sniffing, licking, and biting activity produced in rats by moderate doses of amphetamine have previously been described in the publications cited above. In experiments with other species we have observed varying types of behaviour due to amphetamine; however, in every species a sufficient dose of the drug induced some kind of stereotyped hyperactivity. In the present paper the observed types of amphetamine-induced stereotyped behaviour in some species will be described and its possible relation to stereotyped behaviour observed in the psychiatric clinic will be tentatively discussed.

Methods

The descriptions are based on a constant observation during 4 hrs or more of groups of 2 to 12 animals per experiment. Since the animals'

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behaviour was unchanged for long periods, it was possible to record the observations by hand-writing. The animals remained in their home cages, one or a few (up to three) individuals in each cage. D-amphetamine (Dexedrine®) was given subcutaneously. The doses were calculated as D-amphetamine sulphate.

Results

Rats. A prominent feature of the behaviour after 5 mg/kg D-amphetamine s.c. is continuous sniffing, licking or biting of the cage wire netting, the forepaws or very exceptionally, also its own body; these effects commence 20 to 30 min after the injection and last for 2 to 3 hrs. A detailed description has been given in earlier papers (RANDRUP and MUNKVAD, 1963, 1965, 1966; MUNKVAD and RANDRUP, 1966).

The normal activities, such as moving forwards and grooming, are clearly suppressed during the period of stereotyped activity, but are above normal in the first 15 to 20 min after the injection and again in the final phase 3 to 5 hrs later (RANDRUP and MUNKVAD, 1965a).

These behavioural effects of amphetamine are highly reproducible. In our observations on more than 200 rats given 5 mg/kg s.c. D-amphetamine, all displayed the described stereotyped activity.

All the above observations were made from acute experiments. In one chronic experiment we gave 7 rats amphetamine daily, except on Sundays, for 2 months. After every injection the behaviour became stereotyped, as described above, and the rats appeared normal the following day. Three of the rats, however, were kept together in one cage; sometimes they interrupted their stereotyped activity by fighting each other (attacks, spitting, defense postures, etc.). Fighting only appeared after one month's drug-treatment, and was never seen in acute experiments. Fighting between rats after repeated doses of amphetamine, but not after a single dose, has also been reported by EHRICH and KRUMBHAAR (1937).

Stereotyped sniffing, licking or biting was also produced by derivatives of amphetamine such as methamphetamine (Pervitin®, 10 mg/kg s.c.) and phenmetrazine (preludin®, 50 mg/kg s.c.). The behaviour produced by these two drugs was in all respects very similar to that seen after amphetamine.

Mice. Young males 40 to 60 days old, weighing 28 to 38 g, (N.M.R.I. strain) were observed after doses of 7.5 or 10 mg/kg D-amphetamine s.c. Their behaviour was similar to that of the rats given 5 mg. Locomotion was, however, not as completely suppressed in the middle phase as with the rats. Some of the mice climbed the wire netting of the cage walls and performed their stereotyped sniffing, licking or biting while sitting on the upper part of the wall. As with the rats there were initial and final

phases with increased locomotion on the floor of the cage, some mice running very fast, and grooming. During the end of the initial phase a characteristic simplified form of grooming appeared very frequently; the forelegs were used to wash only the snout.

Only two out of more than the 100 mice which were observed differed from this behavioural pattern. One of these showed no evidence of stereotyped behaviour. The other repeated a more complicated sequence of acts reminiscent of the behaviour of rats described by LÁT (1965), see "Discussion;" this mouse walked round the cage, following a definite track and in addition performed grooming of snout, sniffing the air and standing up against the cage wall, each of these three acts was carried out at a definite place on its route round the cage.

Fig. 1. Guinea-pigs two hours after amphetamine (5 mg/kg s.c.). One bites the edge of the bowl the other became immobile, "froze" as the observer approached to take the picture

When more than one mouse was placed in each cage we often observed fighting and other features of aggressive or defensive behaviour after amphetamine, in agreement with other reports in the literature (LAPIN and SAMSONOVA, 1964; CHANCE, 1948; MOORE, 1963). This behaviour was seen mostly during the first $^1/_2$ to 1 hour after the injection, but after the onset of stereotyped behaviour temporary fighting episodes ("mock fighting") also occurred. Fighting often led to exhaustion and subsequent death of the animals (see also MOORE; LAPIN and SAMSONOVA, 1964); death also occurred, although very infrequently, among mice in individual cages.

Guinea-pigs. Observations were made on twenty-five young male guinea-pigs about 3 months old and weighing 400—500 g, after doses of 5—20 mg/kg amphetamine s.c. All the guinea-pigs showed stereotyped activity. Two of the animals showed continously tossing, vertical move-

ments of the head, and 23 bit continously at the wire netting of the walls, the edge of their clay food bowls (see Fig. 1), straws, and the skin of other guinea-pigs. In four animals the biting was preceded or followed by continous head movements.

Two guinea-pigs performed the stereotype activity only when the observer left the room to watch the animals through a window or the door. With the observer in the room, these animals remained completely immobile and "frozen."

Fig. 2. Cat 20 min after amphetamine 13 mg/kg s.c.

With 5 mg amphetamine per kg (12 animals) the period of stereotypy started $^1/_2$ to 1 hr after the injection and ended about 3 hrs later. After this the activity of the animals gradually became more varied and included locomotion and grooming, which were almost completely absent during the period of stereotypism. During the first $^1/_2$ to 1 hrs after the injection locomotion and grooming were also seen in some animals while others "froze" immediately after the amphetamine injection and remained in this state until they started the stereotyped activity.

Cats. Eight cats (four male and four female) were treated with 13 mg/kg amphetamine i.p. They were all stray cats. The weights were 1.8 to 4.3 kg and ages unknown. All these cats performed head movements which became clearly stereotyped 20 min to 2 hrs after the injection (see Fig. 2) and lasted more than four hours. During this time the cats lay or sat in the cage with very little locomotion, although stereotyped movements of the body were seen in some instances. The head movements were mostly sidewards, the cats appeared to be looking round, and this stereotypy was preceded by a period in which only the eyes moved from side to side. Two cats vomited several times and died about two hours after amphetamine.

Hissing and spitting without interruption of the head movements were observed occasionally. They were very prominent in one cat during a period of one hour beginning 40 min after the injection; this cat was otherwise very tame and friendly, it had been in the laboratory for two months and was well-known to the personnel.

Squirrel monkeys. We observed four squirrel monkeys treated with 1.7 mg/kg amphetamine i.m. All performed stereotyped activity for a prolonged period, but the form of stereotypy varied from individual to individual.

Fig. 3. Monkey No. 4, 75—90 min after amphetamine (2.6 mg/kg) bending down and appearing to stare intensely

No. 1 (female, 410 g) opened and closed continously all four paws while sitting at the edge of a shelf or on a branch.

No. 2 (female, 540 g) made continuous rapid body movements, mostly sidewards but also backwards and forwards. For a period these movements were interrupted by low bows (about 3 per minute) with "staring," resembling the movements described in monkey No. 4 below.

No. 3 (female, 670 g) performed rapid sidewards movements of the body and fore-limbs at a rate of about 30 cycles per minute.

No. 4 (male, 950 g), bent down deeply about 4 times a minute appearing to look or stare intensely (see Fig. 3). Rapid body movements were also seen part of the time.

During the first minutes after the injection of amphetamine the rate of head movements was increased, locomotion decreased and the animals crouched in a corner. The behaviour described above then appeared gradually. Monkey No. 2 appeared sedated during the first hour after the injection, being very quiet with closed eyes most of the time. The movements described became stereotyped $^1/_2$ and $1^1/_2$ hrs after the injection, and continued for $1^1/_2$ to 3 hrs. During this period other activities such as locomotion, grooming and eating were almost completely absent. Except during the periods of "staring" of monkeys

No. 2 and 4, the frequent head movements which these animals normally perform were retained, but increased in rate, from about 1 per sec to 1.5 to 2 per sec so that they became continuous and thus acquired a stereotyped character. Two to four hours after injection the locomotion and grooming began to reappear. Locomotion in monkeys No. 2 and 4 was stereotyped in the beginning, the animals repeatedly followed a definite route in the cage many times, about 6 hrs after the injection their locomotion became more irregular and extended. In monkey No. 3 the locomotion was irregular from the beginning.

The experiment was repeated four months later with a larger dose of amphetamine (2.6 mg/kg) on monkeys no. 3 and 4. Again each of the monkeys performed the same individual form of stereotypy as previously seen but for a longer period of time. No. 3 made a sound which resembled a combined barking and spitting: this was not heard from untreated animals, except when they were caught in order to receive an injection.

Discussion

Other authors, working with similar doses of amphetamine, have described behaviour which resembles our own observations in rats (HAUSCHILD, 1939; VAN NUETEN, 1962; LAPIN and SCHELKUNOV, 1965; SCHELKUNOV, 1964; QUINTON and HALLIWELL, 1963). By courtesy of Drs. QUINTON and HALLIWELL, England, and Drs. LAPIN and SCHELKUNOV, U.S.S.R., one of us has had the opportunity of watching amphetamine treated rats in their laboratories. In both places the behaviour of the rats was closely similar to that observed in our own laboratory. Other forms of stereotypy have been reported. LÁT (1965) showed that rats under amphetamine in smaller doses when put in a new cage may follow a definite track in the cage and repeat this procedure many times, by contrast, untreated rats explored all parts of the cage, following a most irregular track. LÁT also demonstrated a stereotyping effect of amphetamine on the rats' vertical movements ("standing up"). He observed sniffing and biting of cage wire netting too and suggests that the form of stereotypy becomes simpler with increasing doses of drug. These observations, which were all confirmed by LAPIN and SCHELKUNOV (1965) (p. 214), also conform to our experience. ANTWEILER (1942) describes a continuous running in circles by amphetamine-treated rats.

Examples of amphetamine-induced stereotyped responses from rats during more complicated experiments have also been described. Thus in shock-avoidance experiments TEITELBAUM and DERKS (1958) found that amphetamine-treated rats under various experimental conditions drank or turned a wheel steadily even for hours, while untreated rats responded only for a short period after each shock. BÄTTIG (1963) in experiments with a T-maze found that amphetamine, in contrast to

ethanol, sodium barbital, chlorpromazine, meprobamate, imipramine, and caffeine, made the rats show an increased tendency to run to the same side in repetitive trials. CARLTON (1961) has reported that amphetamine decreased alternation between two levers in a reward situation. CHANCE and SILVERMAN (1964), who studied social behaviour in rats, found that amphetamine rendered the exploratory behaviour stereotyped and the emotional behaviour aimless. Their observations seem to agree with ours on mice (see "Results").

Stereotyped activity of mice after amphetamine has also been reported by LAPIN (1966) and by SCHELKUNOV (1964). LAPIN reports that in three strains of mice the forms of stereotypy are different, consisting in one strain of grooming and sniffing, in another of vertical movements and in a third of gnawing.

"Constant purposeless searching head movements" of cats after amphetamine have been briefly mentioned by EMELE *et al.* (1961).

A behaviour which undoubtedly may be interpreted as stereotypy after amphetamine has also been described in other species. Thus in chicks there has been described continuous twitter (KEY and MARLEY, 1962; CLYMER and SEIFTER, 1947; SPOONER and WINTERS, 1966; SELLE, 1940); in pidgeons pecking (SCHELKUNOV, 1966); in dogs continuous rotating movements (CHISTONI and BECCARI, 1940; ACCORNERO, 1947); and in chimpanzees body and head movements, as well as self-picking to the point of producing sores (FITZ-GERALD, 1967).

Clinical observations on the behavioural effects of amphetamine in humans are, of course, much more varied than those made in animal experiments. Investigating psychiatrists have been more interested in psychiatric interviews than in behavioural observations of the undisturbed patients. Nevertheless, some cases of clearly stereotyped activity are described in the literature: for example, in the monograph on methamphetamine psychosis by TATETSU, GOTO and FUJIWARA (1956) there is a description of two patients' behaviour immediately after hospitalization: ". . . their incomprehensible, odd and very unnatural movements were constantly, identically and energetically repeated." The picture of one of these patients swhows a man in a boxing attitude (p. 81). A more detailed description of odd movements of body, limbs and head, which are "constantly and identically repeated" is given in their case history No. 3 p. 150–151. These unusual movements were "greatly enhanced" when, two days later, an intravenous injection of 30 mg methamphetamine was given. Patient No. 5 repeated the same few sentences" . . . constantly and identically. She does not stand up or move, but keeps sitting while continuously talking." (p. 157). In a summary of the monograph in German, TATETSU (1960) states: "Unter die katatone Sympto-

men sind besonders zu rechnen: Stupor, Hyperkinesie, Katalepsie, Manieren, *Stereotypien* (italics by us), Negativismus, impulsive Gewalttat und Grimassen."

Clear cases of stereotyped behaviour in amphetamine psychosis are also described in two other monographs on the subject, i.e. that of BONHOFF and LEWRENZ (1954) (p. 104) and that of CONNELL (1957) (case 20).

Recently RYLANDER (1966) published a study of 150 patients, who had abused preludine (phenmetrazine), a close analogue of amphetamine (see "Results" section on rats). He noticed a symptom called "pundning" in Swedish patient-slang. This is described as compulsive or automatic continuation for hours of one aimless activity, such as sorting objects in a handbag, manipulating the interiors of a watch, polishing fingernails to the point that sores are produced, etc. The symptom was first overlooked, since the patients seldom report it spontaneously, but when investigated, it was found in 29 out of 43 cases.

In many other case reports of amphetamine psychosis, repetitions of compulsive and purposeless acts are described, but the descriptions are so incomplete that it cannot be decided whether the behaviour satisfies our definition of stereotyped activity as given above in the introduction. TATETSU *et al.* (1956), SANO and NAGASAKA (1965), CONNELL (1957 and 1958), SHANSON (1956), KALUS *et al.* (1942), BONHOFF and LEWRENZ (1954), KALUS (1950), BINDER (1945), DAUBE (1942), STAEHLIN (1941), MARTIMOR (1955), NORMAN and SHEA (1945), GREVING (1941), HAGUENAU (1947), GERICKE (1945), SCHNECK (1948), KALANT (1966).

The doses of amphetamine which have caused psychosis are of the same order of magnitude (1—20 mg/kg) as those reported above in the animal experiments. The psychosis is usually found in addicts, but several cases caused by a single dose are on record (CONNELL, 1957, 1958; BEAMISH and KILOH, 1960; HAMPTON, 1961; SHANSON, 1956; KALANT, 1966), in some of the chronic cases acute psychotic effects of a single dose are reported (TATETSU *et al.*, 1956, case 3; CONNELL, 1957 in Appendix B case 13 p. 93—94, case 20 p. 154—155, case 31 p. 282, case 42 p. 398; KALUS *et al.*, 1950 case 1; STAEHLIN, 1941). The above mentioned clinical reports on cases of amphetamine psychosis repeatedly describe phenomena closely resembling those of schizophrenia and misdiagnoses were made. The diagnoses were corrected when the intake of amphetamine was discovered and discontinuation of the drug led to remission of the psychotic symptoms. It should, however, be considered that also schizophrenics may ingest amphetamine with the result that psychotic symptoms including catatonia and stereotypy are intensified. Such cases are also described in the literature (BELART, 1942; DELAY *et al.*, 1947).

It may be that studies of the amphetamine effects will lead to results of interest for basic research into the psychoses. This has been our

principal idea and the observation that stereotyped behaviour has also been described in man may support this point of view.

Other authors (UTENA, 1961; KARLI, 1960; BELART, 1942) have also indicated that studies of the effects of amphetamine might be of interest for psychosis research. UTENA (1961) compared amphetamine-induced abnormal behaviour in man and animals, but while we have studied the acute effects of a single dose, UTENA has concentrated on behavioural features observed during the first weeks after discontinuation of prolonged methamphetamine intoxication.

Summary

Experiments with chickens, pidgeons, mice, rats, guinea-pigs, cats, dogs, squirrel-monkeys and chimpanzees show that stereotyped activity can be produced by amphetamine in doses of 1—20 mg/kg in all these species ranging from birds to primates.

In man amphetamine in similar dose, i.e. higher than the therapeutic doses, can produce a psychosis, which so closely resembles schizophrenia, that misdiagnoses have been made. All the known symptoms of schizophrenia are reported, including stereotyped activity.

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