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Dopamine-sensitive alternation and collateral behaviour in a Y-maze: Effects of *d*-amphetamine and haloperidol

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Abstract. The degree of alternation of arm choice in a Y-maze was examined on 15-min tests over 4 days in rats treated (IP) with saline, amphetamine (0.5 or 2.0 mg/kg) or pretreated with haloperidol (0.08 mg/kg) in each condition prior to test. On day 1 amphetamine-treated animals chose arms at random, but from day 2–4 those receiving the higher dose perseverated their choice. Controls maintained alternation. These effects could be prevented by haloperidol pretreatment. Amphetamine treatment increased the frequency of rearing at the middle, choice-point of the maze more than at the end of an arm. The increase at the mid-point was suppressed by haloperidol pretreatment from day 1 and at the end of an arm from day 2. Amphetamine induced an increase in head-turning/"looking" that was suppressed by haloperidol from day 2. The effect of haloperidol in increasing the duration of an item of looking or rearing at the end of an arm also started later in testing. Two effects are postulated to have occurred: (i) a conflict on day 1 between novelty-controlled sensory or attentional effects that leads to an alternation of arm choice and amphetamine-induced dopaminergic activity that facilitates an alternation of behavioural responses. The result was random choice and increased rearing at the choice point. (ii) On days 2–4 the drug-induced effects on switching motor responses came to control behaviour.

Key words: Amphetamine – Haloperidol – Dopamine – Y-Maze – Alternation – Rearing – Collateral behaviour – "Switching" – Novelty – Attention – Rat

When placed in a Y- or a T-maze rodents usually visit the three arms one after the other. If this behaviour occurs with a frequency significantly greater than 50% it is called spontaneous alternation. This behaviour has long been regarded as an exploratory response (Dennis 1939; Montgomery 1954; Dember 1961) where the preference is controlled by novel stimuli and habituation to the most recently visited arm (Carlton 1963; Douglas 1972; Kokkinidis and Anisman 1980).

A reduction in the frequency of alternation has been reported after damage to limbic structures (Dalland 1970; Douglas 1972) and treatment with agents interfering with noradrenergic, cholinergic and GABAergic neurotransmission (review, Hughes 1982). Only septal lesions (Clody and Carlton 1969) and treatment with dopaminergic agonist drugs (Adkins et al. 1969; Kokkinidis and Anisman 1978a; Katz and Schmaltz 1981) have been reported to result in a perseveration of choice of the maze arm at frequencies below 50%.

Both intra- and extra-maze cues have been shown to influence the frequency of alternation (Glanzer 1953; Douglas 1966; Kokkinidis and Anisman 1978a). The reduction in the frequency of alternation by lesion damage (Markowska and Lukaszewska 1981) or treatment with dopaminergic agonists (Katz and Schmaltz 1981) has been attributed to anomalous sensory or attentional control. Certainly, explanations in terms of effects on memorial processes seem unlikely in so far as animals that alternate or perseverate at a level significantly different from 50% would appear to have retained information about the arm most recently visited (Hughes 1982). However, recent studies of choice behaviour have considered the possible effect of the catecholaminergic agonist amphetamine on response bias (Eckerman et al. 1980; Evenden and Robbins 1983).

We were interested in the reported influence of dopaminergic agents on putative, attention-related function. Therefore, we examined the effect of amphetamine treatment on choice behaviour in the Y-maze, and we report on the dopaminergic component to the changes recorded as shown by pretreatment with the dopaminergic antagonist haloperidol. The performance of rats was recorded over the relatively long period of 15 min on 4 successive days. We did this to determine the effect of novelty on choice on the 1st day and whether the strategy of choice, putatively guided by the relatively novel stimuli of the least recently visited arm, changed with exposure to the maze for animals that were alternating or perseverating their choice. For mice it has been reported that perseverative choice habituated towards chance levels with repeated amphetamine treatments (Kokkinidis and Anisman 1978a, b).

Rearing and head-turning/"looking" behaviour at the choice point between arms were also recorded. The first reason for this was that the frequency of these "observing responses" seemed likely, from an ethological point of view, to be correlated with putative attention-related changes of stimulus processing. Secondly, increases in collateral or displacement rearing have been recorded from rats with increased mesolimbic dopaminergic activity on a

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search task (Oades 1981, 1983) and similar increases in rearing have been interpreted to support the hypothesis of an attentional dysfunction in rats learning a delayed alternation task (Simon et al. 1980).

We show that novelty of the first test did affect arm choice in rats (for mice, Kokkinidis and Anisman 1978a), but, in contrast to these authors, control levels of alternation and amphetamine-induced perseveration were both maintained over days 2–4. We show not only that the frequency of rearing was increased by amphetamine (Makanjuola et al. 1977; Fray et al. 1980) but that collateral behaviour at the choice point was particularly affected. The perseveration of choice and the increased collateral behaviour at the choice point were prevented by pretreatment with haloperidol. The effects of the pharmacological treatment that became overt after the first test are interpreted in terms of changing motor patterns of response.

Materials and methods

Results are reported for 36 male Sprague-Dawley rats (IFFA-Credo, Lyon) weighing 200–300 g. The animals arrived in the laboratory at least 1 week prior to testing, were housed singly in a temperature- and humidity-controlled room on a 12-h light/dark (08:00–20:00 h) schedule and were handled daily.

Drug treatment. Animals were treated (IP) on 4 successive days with vehicle (0.9% saline), *d*-amphetamine sulphate (Coop. Pharm. Francaise, Melun) or haloperidol (Haldol solution – physiological saline, Janssen-le-Brun, Paris). There were six animals per group. *Group S* received saline, *group A* a low dose of amphetamine (0.5 mg/kg) and *group B* a higher dose (2.0 mg/kg) 40 min before testing. Three more groups received haloperidol treatment (0.08 mg/kg) 60 min before one of the above treatments (*groups SH, AH,* and *BH* respectively). Injection volumes were 1.0 ml/kg. Data are not reported for animals treated with 5 mg/kg amphetamine, since they showed stereotyped behaviour to the exclusion of exploration. The behaviour of animals pretreated with 0.02 mg/kg haloperidol did not differ significantly from that vehicle-injected controls.

Test procedure. A 15-min test was conducted on 4 successive days (13.30–17.30 h) in a Y-maze (40 × 15 × 35 cm) made of wood with a brown vinyl finish. The floors and walls were wiped with a damp then a dry cloth after each test. A mirror was suspended at an angle 1 m over the maze to permit recording of the behaviour at a distance (2 m). The maze was in a sound-attenuated room under dim illumination. White noise (66 dB, A) was played to mask extraneous noise. Animals were brought in their home cage to the room immediately prior to test. Animal codes were changed (KT) just prior to the test so that behavioural observations were made (RO) without knowledge of the treatment.

The following responses were recorded on a push-button box and registered on a Digital PDP 11 computer: identity of arm choice, duration and number of arm visits, number of squares crossed (three/arm were marked on the floor), rearing at the end of an arm and at the mid-point where the arms meet and "looking" left and right at the mid-point.

Behaviour and statistical treatment. Rearing was scored when the forepaws left the floor. Looking was recorded when the animal turned its head to the left or the right of the longitudinal axis of the body. It was only scored at the choice point. An arm visit was recorded when a rat moved all four paws into the arm. Perseveration of choice refers to when an animal entered the most recently visited arm and alternation when it entered the least recently visited arm. Alternation and perseveration mean that more or less than 50% (respectively) of visits during a test were to the least recently visited arm. Standard errors and values for χ^2 are presented, although the latter statistic can be biased by the variable number of arm visits (Kokkinidis and Anisman 1978a). Since this presentation is mainly concerned with the relative effects of drug treatment, data were analysed by multifactor analysis of variance (ANOVA) with repeated measures where appropriate. Tests were performed firstly for drug treatments over days and secondly for performance on separate days for amphetamine- and haloperidol-treatments to provide the variance for post hoc comparisons by the Newman-Keuls test (NK) where overall significance had been achieved.

Results

Alternation. The S group of animals alternated visits to the three arms of the Y-maze on day 1 (χ^2 43; $P < 0.01$) and maintained this level of alternation to day 4 (Fig. 1). Amphetamine-treated animals chose closer to random on day 1 (χ^2 2.9), but the B group perseverated arm choice from day 2 (χ^2 21; $P < 0.01$) to day 4 (χ^2 30; $P < 0.01$). The A group tended to perseverate choice on day 1 (χ^2 5.8) but thereafter chose at chance levels. Pretreatment with haloperidol clearly reduced the effect of amphetamine. Pretreated animals sometimes alternated around 50% (BH, days 2 and 4) and sometimes at significantly higher levels (χ^2 for AH, day 1–4, 45, 37, 19, 19 and for BH, day 1 and 3, 26, 24: $P < 0.01$).

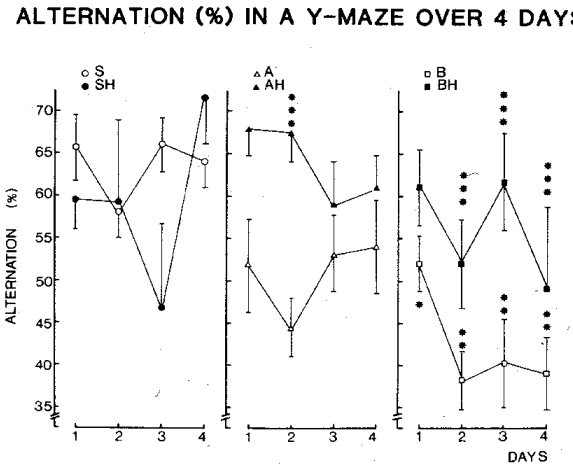

Fig. 1. The effect of vehicle, amphetamine and haloperidol treatments on the percentage alternation of arm-choice (ordinate) in a Y-maze over 4 successive days: amphetamine reduces alternation dose-dependently and haloperidol pretreatment inhibits this effect. *S* saline; *A* 0.5 mg/kg and *B* 2.0 mg/kg amphetamine, *H* 0.08 mg/kg haloperidol pretreatment. *Bars* represent SEM. *S vs B $P < 0.05$, **S vs B $P < 0.01$, ***B(A) vs BH (AH) $P < 0.05$

A significant difference between saline and drug treatment occurred already on day 1 (group/treatment, *df* 132, 2; *F* 5,1; $P < 0.02$: treatment/days, *df* 6, *F* 2.5; $P < 0.03$). This became more marked as group B perseverated (NK, day 1 $P < 0.05$; day 2–4, $P < 0.01$). The differences between S and A groups were not significant. The preventive effect of haloperidol pretreatment (*df* 11, 1; *F* 8.8; $P < 0.04$) became significant as group B perseverated (NK, $P < 0.05$).

Locomotion. There was a dose-dependent increase in locomotion for groups S, A, and B on each test as measured by the number of squares crossed (Fig. 2: *df* 132, 2; *F* 4.8; $P < 0.02$) and the number of arms visited (for S, A and B respectively, days 1–4: 33–31, 43–48, 57–53). Repeated haloperidol treatment decreased locomotion (*df* 11, 1; *F* 18.7; $P < 0.002$) and the number of arms visited (SH, AH, and BH respectively, days 1–4: 32–15, 47–39, 51–22). In contrast to the frequency of alternation, for group AH neither measure of locomotion was significantly affected by haloperidol pretreatment.

Rearing. The frequency of rearing was elevated after the high dose of amphetamine (group B). This was prevented by pretreatment with haloperidol (total rears/treatment; *df* 132, 2; *F* 3.8; $P < 0.04$: Fig. 3).

Considering rears at the end of an arm separately, the effect of amphetamine treatment proved more variable. Increased rearing was significant on day 2 (NK, B vs S, $P < 0.05$) but not on days 1 or 4. By contrast, rearing at the mid-point of the maze was consistent over all tests for all groups. In this case the B group reared more then the BH (NK, $P < 0.01$) or S groups ($P < 0.05$) on all tests.

To emphasize this point, Table 1 shows the ratio of the number of rears at the mid-point to those at the end of an arm. Whereas groups A and B usually showed ratios larger than 0.5, the vehicle- and haloperidol-treated groups showed ratios less than 0.5. Haloperidol prevented the appearance of amphetamine-induced rearing (*df* 11.1; *F* 17.6; $P < 0.002$/ NK, B vs BH or S, $P < 0.05$).

"Looking". One might expect haloperidol treatment to increase and amphetamine to decrease the frequency of "looking", since this response was sometimes absent in a fast-moving animal early in a test. In fact, amphetamine increased the frequency of looking in a dose-dependent manner and haloperidol prevented the effect (Fig. 4: *df* 23, 3; *F* 9.2; $P < 0.001$: *df* 72, 3; *F* 3.5; $P < 0.02$). It may be noted that this would not be expected if there were a strong behavioural competition between looking and rearing.

The increased frequency of looking in group B was marked from day 1 (NK, B vs S, $P < 0.05$), but haloperidol did not start to prevent this effect until day 2 (NK, B vs BH, $P < 0.05$). Even in the S group haloperidol tended to decrease the frequency of looking only on later tests (day 4, $P < 0.05$). No consistent differences were recorded for the frequency with which animals looked to one or the other side after any of the treatments.

Table 1. Ratio of the number of rears recorded at the choice point compared to the end of an alley in a Y-maze

Group	Day			
	1	2	3	4
S	0.32 (0.04)	0.39 (0.08)	0.50 (0.08)	0.46 (0.06)
SH	0.36 (0.05)	0.46 (0.06)	0.28 (0.08)	0.28 (0.06)
A[a]	0.50 (0.05)	0.59 (0.12)	0.36 (0.03)	0.72 (0.22)
AH	0.33 (0.03)	0.49 (0.10)	0.42 (0.11)	0.37 (0.09)
B[b]	0.60 (0.11)	0.58 (0.09)	0.57 (0.14)	0.84 (0.20)
BH	0.29 (0.06)	0.31 (0.06)	0.33 (0.11)	0.25 (0.07)

[a] A vs saline or haloperidol treatment $P < 0.05$ (days 1, 2, and 4)
[b] B vs saline or haloperidol treatment $P < 0.01$ (days 1–4)
SEM in parentheses

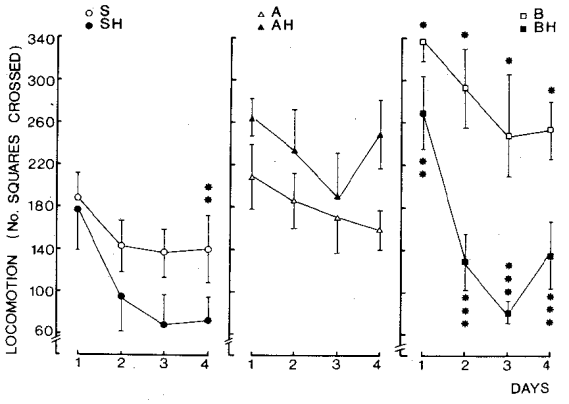

Fig. 2. The effect of vehicle, amphetamine, and haloperidol treatments on locomotion (the number of squares crossed, three arm) in a Y-maze over 4 successive days: amphetamine treatment increases locomotion dose-dependently: pretreatment with haloperidol can suppress this (not group A/AH) and becomes more effective over days (SH & BH). *Bars* represent SEM. For codes see Fig. 1 legend. *S vs B $P < 0.05$, **B(S) vs BH(SH) $P < 0.05$, ***B(S) vs BH(SH) $P < 0.01$

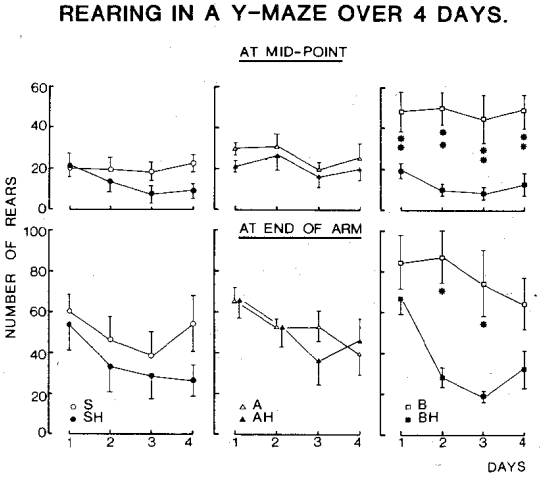

Fig. 3. The effect of vehicle, amphetamine and haloperidol treatments on the frequency of rearing at the middle, choice point (*upper figure*) and at the end of an arm (*lower figure*) of a Y-maze over 4 successive days. The higher dose of amphetamine increases rearing at both points, but a clear significant increase on all four days is only shown at the mid-point. The effect is suppressed by pretreatment with haloperidol. *Bars* represent SEM. *B vs S (BH) $P < 0.05$, **B vs S $P < 0.05$, and B vs BH $P < 0.01$

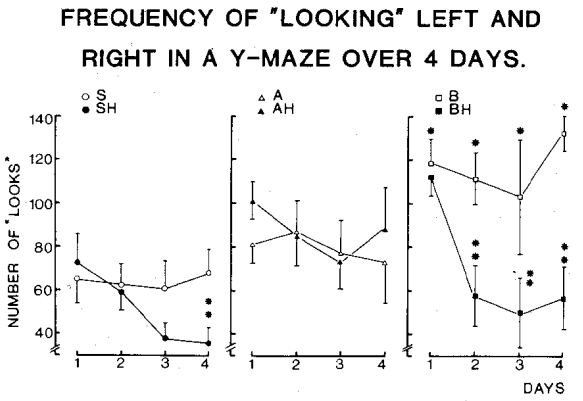

Fig. 4. The effect of vehicle, amphetamine, and haloperidol treatments on the frequency of head turning/looking at the middle choice point between the arms of a Y-maze on 4 successive days. As with rearing at the end of an arm, amphetamine increases the number of looks from day 1 and haloperidol suppresses this effect from day 2 for the group receiving the higher dose of amphetamine *Bars* represent SEM. *B vs S $P < 0.05$, **B vs BH $P < 0.05$, and S vs SH $P < 0.05$

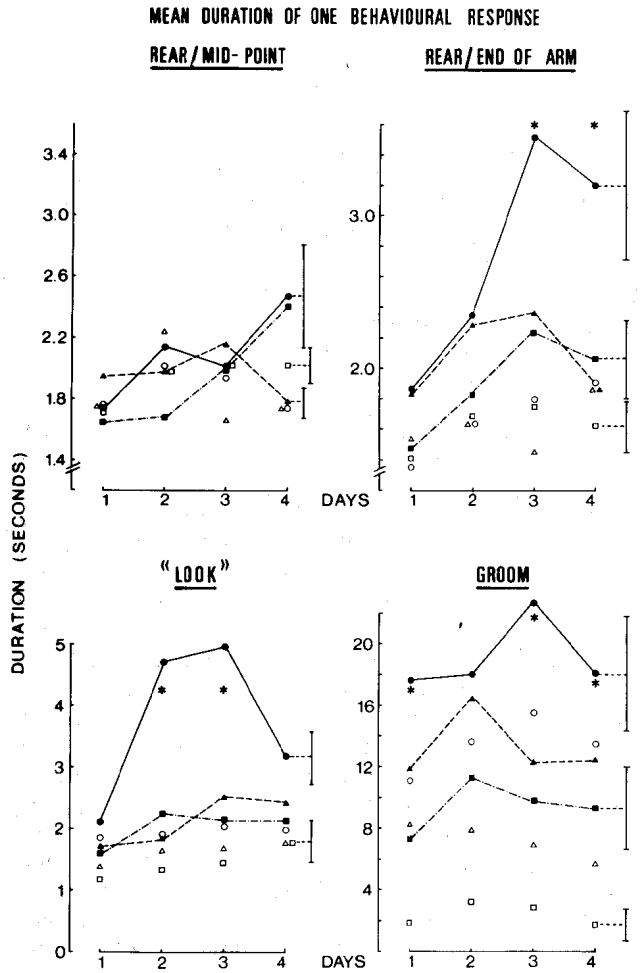

Fig. 5. The effect of vehicle- (○), amphetamine-(△ 0.5 mg/kg, □ 2.0 mg/kg) and haloperidol pre-treatment (●, ▲, ■, respectively) on the mean duration (s) of one behavioural response of four types of behaviour recorded in a Y-maze are shown over 4 successive days. Except for rearing at the mid-point, haloperidol increases the response duration (*$P < 0.05$). The effect is attenuated by subsequent amphetamine treatment. Selected SEMs are shown to the right of each diagram for day 4

Measures of duration. Measures of the mean duration for one rear or one "look" show:

1. There was no clear effect of drug treatment or test day on rearing at the choice point of the maze (Fig. 5).

2. Haloperidol treatment alone increased the duration of rearing at the end of an arm and of looking (*df* 11, 1; F 10.9; $P < 0.008$: F 8.2; $P < 0.016$; respectively). These effects became significant on later test days for rearing (NK, s vs SH, day 3, 4; $P < 0.05$) and for looking (day 2, 3; $P < 0.05$).

3. This effect of haloperidol was counteracted by subsequent amphetamine treatment in a dose-dependent manner (look, *df* 132, 2; F 5.7; $P < 0.01$). The variability of the scores precluded finding significance according to the NK test between vehicle- and haloperidol-treated groups receiving the *same* dose of amphetamine.

Discussion

Spontaneous alternation over a 15-min test in a Y-maze was maintained by rats over 4 successive days. Amphetamine treatment induced random choice on the first test. At a low dose (0.5 mg/kg) choice remained random, but at a higher dose (2.0 mg/kg) a perseveration of choice was maintained from day 2 to 4.

The levels of alternation and perseveration and the effect of novelty on the first test were similar to those reported for mice (Kokkinidis and Anisman 1978a). Signs of an habituation of perseveration over repeated tests reported by these authors using 5 and 10 mg/kg (IP) over five 15-min tests were not observed. Several procedural reasons could account for this, but we suspect that distant extra-maze cues may have been more perceptible for the larger animal. This may have helped animals to identify the arms and maintain a perseveration of choice.

Kokkinidis and Anisman reported that tolerance was not evident in mice after three daily injections of amphetamine. The present study did not specifically address this issue, but the consistency of the data over days 2–4 indicates that the treatment regime was too short for signs of tolerance to be shown. Further, groups of animals were treated, as in this report, but were tested for the first time on day 4. There was no difference between their behaviour and those tested on the 1st day of treatment (Oades et al. submitted). Thus, it is unlikely that the maintenance of perseverative choice was a direct result of the effects of multiple injections on other behaviour (e.g., Stereotypy; Kokkinidis and Anisman 1981, p 454).

Haloperidol pretreatmet prevented amphetamine-induced perseveration. The decrease of locomotion recorded under haloperidol treatment did not appear to account for this change (cf results for group A). Kokkinidis and Anisman (1978a) reached a similar conclusion.

As long as a rat has access to and can recall cues that indicate it entered an unrewarded arm, its next choice will be directed to the unexplored or least recently visited arm (Livesey et al. 1981). For animals that alternate or perseverate it is likely that the mechanisms necessary for forming and using the memory for the most recently visited arm are intact. This may not be true for those choosing at chance levels (Hughes 1982). Postulation of a memorial deficit on day 1, absent on days 2–4, is not a reasonable explanation for our observations.

Amphetamine treatment may affect the "access to" or utilization of cues governing choice. An attenuation of the control of choice by novel stimuli could not, alone, account for our results, since this would lead to random rather than to perseverative choice. An increase in neophobia can be ruled out, because this would lead to a suppression of exploration that was not observed (Kokkinidis and Anisman 1981). Three types of "sensory persevaration" may be postulated: a preference for a particular intra/extra maze cue, for familiarity of an arm or for a category of cues (e.g., place). These interpretations seem unlikely because arm preferences, as shown by sequences of perseverative choices, vary both between individuals and during a test for a given individual. To demonstrate whether any of these hypotheses could *partially* account for a perseveration of choice would require manipulations of specific stimuli that we did not attempt. Nonetheless, hypotheses which maintain that a sensory selection or attention-related mechanism may guide the choice of the least recently visited or more novel arm (Douglas 1972; Kokkinidis and Anisman 1980) are supported by finding that the emergence of perseverative choice is retarded on the 1st test day independent of the number of treatments.

Drug-induced changes in the execution of motor patterns present an alternative explanation for a perseveration of choice. The effect of amphetamine cannot be explained by ballistic tendencies of a fast-moving animal, because the treatment increased the time spent and the behaviour shown at the choice-point between arms. But it should be noted that a perseveration of choice involves an alternation of body turns (Katz and Schmaltz 1981). Thus, if a rat has turned left out of one arm, then to return to this arm it must necessarily turn right. Amphetamine treatment may facilitate a switch in the direction of turning, as has been shown in operant situations (Evenden and Robbins 1983). According to this interpretation, only when the novelty of the maze stimuli was most salient (day 1) was the drug-induced tendency to switch turning responses attenuated.

In apparent contrast to this explanation, Jerussi and Glick (1974) reported that amphetamine treatment enhanced rotation in one direction. But such an unhindered, unidirectional circling, as found in a circular alley, does not occur when the same animals are placed in a Y-maze (Kokkinidis and Anisman 1977). Further, measures of the direction of "looking" in the present experiment showed no evidence of a preference for one side. A second difficulty seems to be posed by the finding of Kokkinidis and Anisman (1977) that whereas perseverative choice follows IP administration, alternation follows unilateral ICV administration. However, whereas amphetamine will be widely distributed after IP administration, there are difficulties in interpreting the effects of local injections that will cause an imbalance of transmitter metabolism between systems close to or remote from the ventricle (Cools and Van Rossum 1980; Hannigan et al. 1984). The results of local treatments are of interest for determining differential contributions of brain systems to the appearance of behaviour in a Y-maze, but less significant for determining the dominant type of behavioural organization following the peripheral administration of amphetamine.

An explanation of perseveration in terms of switches or changes of the direction of turning receives some support from an analysis of other behaviour in the Y-maze. Our results seem to confirm those of Meyerson and Hoglund (1981), who showed a correlation between the frequency of rearing and scanning side-to-side head movements. This may be oversimplified. An increased frequency of rearing after amphetamine treatment on the first trial occurred only at the choice point. This was suppressed by haloperidol treatment. But the increased frequency of looking was not suppressed by haloperidol until the second test. The effect of haloperidol in prolonging a single look or rear at the end of an arm did not occur until the second or third test. These results suggests two conclusions. The pharmacological action of haloperidol enhances the duration of a component of behaviour, whereas amphetamine increases its frequency (i.e., switching the behaviour on and off, Norton 1973). These effects are more clearly distinguishable when the maze has lost its novel aspect (day 2–4) and support the explanation of the amphetamine effect in terms of switching (e.g., rearing, on/off; turning, left/right).

Nonetheless rearing (haloperidol-sensitive) and looking (haloperidol-insensitive) at the choice point on the first test may relate to the perception of novel stimuli that control choice in a normal animal. Their increased frequency after amphetamine may reflect a search for these stimuli, an attentional response or perhaps a collateral response. A collateral response, rather like the ethological notion of a displacement activity (Hinde 1979, p 406), is a behavioural element that arises during behavioural conflict and is often irrelevant to resolving the conflict. In this case the sources of conflict are the two opposing tendencies; to alternate to novel sensory cues and to alternate/switch turning patterns (facilitated by amphetamine). The appearance of collateral behaviour at the choice point may be faciliated by a non-specific increase of arousal or vigilance (see: earlier discussions of a dopaminergic component in amphetamine-induced arousal in Broadbent 1971; Horvath and Meares 1974). As the rearing element is sensitive to dopaminergic mechanisms, this interpretation may also explain the increase and decrease in rearing found, respectively, after increases in dopamine utilization or depletion in dopamine levels in the nucleaus accumbens during task performance (Simon 1981; Oades 1983; Kalivas et al. 1983; Taghzouti 1983). Furthermore, the frequency of experimental analogues of displacement behaviour are reported to be sensitive to dopamine-depleting lesions (Robbins and Koob 1982).

In conclusion, there is strong reason to believe that alternation in a Y-maze is affected by attention to stimulus factors. When these factors are novel, they can compete with changes of dopamine activity that promote changes of the motor pattern of behaviour (turning, looking). It is likely that an increase in the release of dopamine may be responsible for the perseveration of arm-choice, since this tendency is prevented by the dopamine receptor-blocking agent haloperidol. It seems unlikely that the alternation of choice itself, as a sensory or attention-controlled phenomenon, has a prominent dopaminergic component, because haloperidol treatment alone did not affect levels of choice.

We propose that collateral rearing at the choice point may reflect the competition between the control of behaviour by novel stimuli and the control exerted by the pharmacologically induced tendency to switch motor patterns of response. This hypothesis that dopaminergic activity can be related to switching in neural systems and

changes in behavioural systems has been elaborated elsewhere (Robbins and Everitt 1982; Oades 1985), but requires further experimental study for confirmation.

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