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DOPAMINERGIC AGONISTIC AND ANTAGONISTIC DRUGS IN THE VENTRAL TEGMENTUM OF RATS INHIBIT AND FACILITATE CHANGES OF FOOD-SEARCH BEHAVIOUR

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The proposal that an increase of dopaminergic activity in the mesocorticolimbic pathway increases the probability of behavioural change is tested. Rats were trained to search for 4 food pellets in a 16-hole board arena. Groups of rats received lesions of the ventral tegmental area (VTA) or injections of spiroperidol or apomorphine into the VTA after sessions 4 and 7 (max. 9 sessions). Spiroperidol-treated and lesioned animals changed their preferred food-hole visit sequences more often than controls. After session 7 the apomorphine-treated group changes less often than controls. It is proposed that increased dopaminergic activity in the mesocorticolimbic pathway facilitates changes of behavioural strategy.

Lesions of the ventral tegmental area (VTA) that include the dopaminergic A10 neurones result in the increased occurrence of irrelevant or collateral behaviour. Simon et al. [11] described an increase of stopping, rearing and turning while rats were learning a delayed alternation task. An impaired habituation of rearing and grooming on a hole-board search task has been reported after VTA damage [5] and injection of spiroperidol into the VTA [6]. Lesion of the nucleus accumbens, to which the VTA projects [10], resulted in an attenuation of irrelevant (displacement or adjunctive) drinking [8].

Koob et al. [2] suggested that damage to the dopaminergic mesocorticolimbic pathway that ascends from the VTA results in an impaired ability to switch between behavioural activities. Oades [6] proposed that the learning deficit in a hole-board search task following treatment of the VTA with spiroperidol could be explained by the reported increase of mesocorticolimbic neural activity that follows this treatment [1] resulting in interference or too much switching between search strategies. I report here an analysis of hole visit sequences on the search task as a test of this hypothesis.

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Fifty Long-Evans hooded rats were maintained separately but in visual, auditory and olfactory contact on a 12 h light/dark cycle at 23 ± 2 °C. Cannulae (outer diam. 0.71 mm) were chronically implanted into the VTA or 2 mm above (3.4 posterior to bregma, 0.6 lateral, 6.4 or 8.4 below the skull; bite bar +0.5 mm). The first group received a mechanical lesion (n = 12, ref. 4). The rest of the animals were divided into 3 groups: those to be treated with spiroperidol (Sp, n = 12, 2 μg/0.5 μl), with apomorphine (Ap, n = 12, 2 μg/0.5 μl) or vehicle (C, saline or pH adjusted 0.1 M tartarate) (Fig. 1).

After one week of recovery the animals were habituated to the hole-board over the second week [4,7] and then deprived of food. The grey plastic hole-board (70 × 70 cm) contained 16 holes in a 4 × 4 array and 10 cm apart [4,7]. The apparatus was illuminated by a 10 W red bulb suspended 50 cm above the floor in a sound attenuation chamber. During testing 4 food pellets (Noyes 35 mg) were placed consistently in the same 4 holes (A1, B3, C2 and D4 of the array). Animals were tested at 80% of their predeprivation body weight. They entered the arena from a start box half way along one of the walls. A trial ended when all food pellets had been eaten. There were 10 trials in a session (interval 45 sec). One session was performed in the morning and one in the afternoon (interval >4 h). Up to 9 sessions were performed in the week following daily habituation to the test procedure and apparatus. Injections were carried out 15 min before sessions 4 and 7. Rearing, the

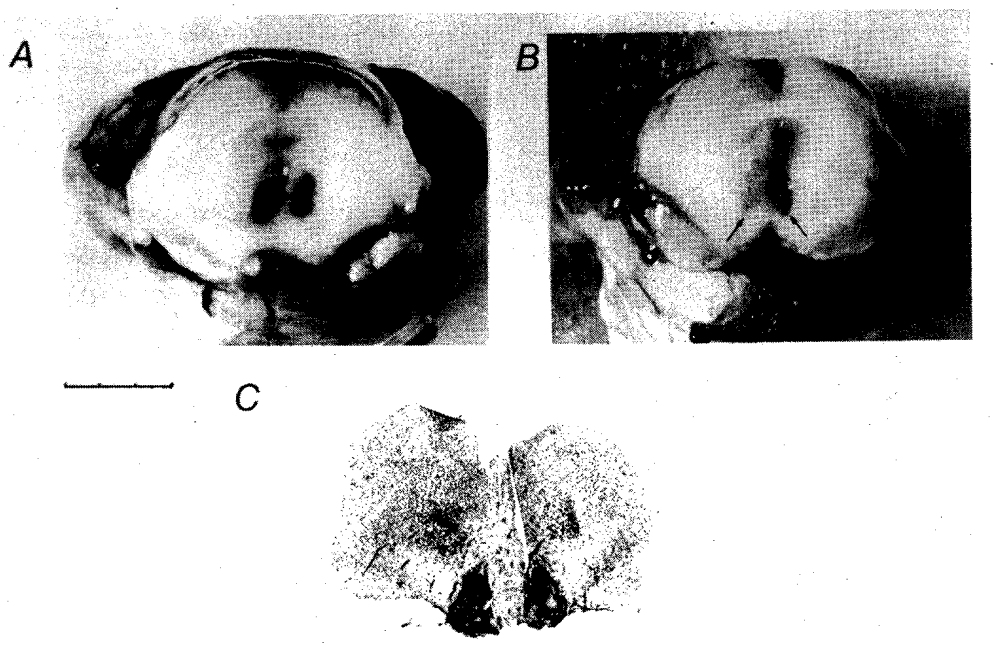

Fig. 1. The sites of injection in the posteroventral midbrain tegmentum of 3 rats are shown. 0.5 μl erythrosin dye was injected before sacrifice. A (dorsal site) and B (intermediate site) are photographs taken in the transverse plane on dissection; C (ventral site) is a 40 μm transverse section stained in cresyl violet. The scale bar is 3 mm. Flow of the dye into the cannula track on withdrawal at dissection is seen in B.

sequence of hole visits and the trial duration were recorded. Data were tested according to the Kruskal–Wallis analysis of variance (KW) or Mann–Whitney U-test (MW) [9].

After spiroperidol treatment many more errors (empty hole visits) were made than after apomorphine or vehicle treatment (Fig. 2, $P < 0.01$, $H > 10$, KW). An increased number of errors has been reported to follow VTA damage [4] and this probably reflects an increase in the number of hole visits rather than an increase of locomotion per se [5]. (Percentage scores show that rats that find food rapidly at first, irrespective of treatment, make fewer errors later in training. This is significant, for all rats tend on one trial in a session to change their hole visit sequence and incur an exceptional number of errors. This number is proportional to how well the individual has learned the task.)

Normal rats develop a preferred sequence of food-hole visits (strategy) that by session 9 will be repeated on 7–8 out of 10 trials [5]. The actual sequence (e.g. ABC or BCA) is individually different. In the current series, animals receiving apomorphine or the vehicle developed a conservative preferred sequence to the same degree

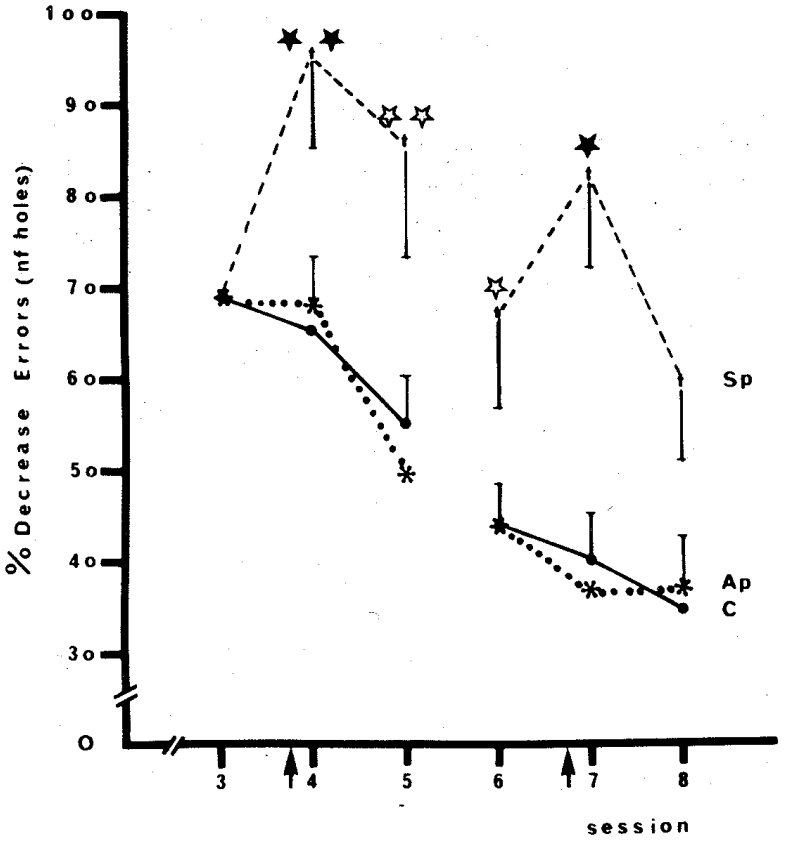

Fig. 2. The percentage decrease of errors (empty hole visits) across sessions (10 trials/session) is shown for spiroperidol (Sp)-, apomorphine (Ap)- and vehicle-treated rats (C) while learning to find 4 pellets of food consistently located in 4 of 16 holes in a hole-board arena. Injections into the VTA took place 15 min before sessions 4 and 7. $^{**}P < 0.001$, $H = 18$, KW; $^{*}P < 0.01$, $H = 10$, KW.

as unoperated controls (Fig. 3). The acquisition, of a preferred strategy was impaired after spiroperidol treatment on session 4 compared to the apomorphine-treated group ($0.001 < P < 0.01$, $H = 8.3$, KW). The control group was slightly impaired but, in contrast to the spiroperidol-treated group, recovered rapidly. After treatment on session 7 the spiroperidol-treated group was markedly impaired by comparison with the vehicle- and apomorphine-treated groups ($P < 0.001$, $H = 18$, KW). The frequency of repetition of the preferred strategy by the lesioned group (about 3 times per session) was significantly less than for the control group ($P < 0.02$, $K = 5.6$ KW) [6]. Clearly lesion or the application of spiroperidol to the VTA increased the number of changes of strategy *between trials of a session*. Was there an increase in the number of changes between sessions irrespective of how often the preferred strategy was repeated within a session?

A larger proportion of animals with VTA damage or neuroleptic treatment than of controls changed their preference on treatment sessions 4 and 7 (Table I, left).

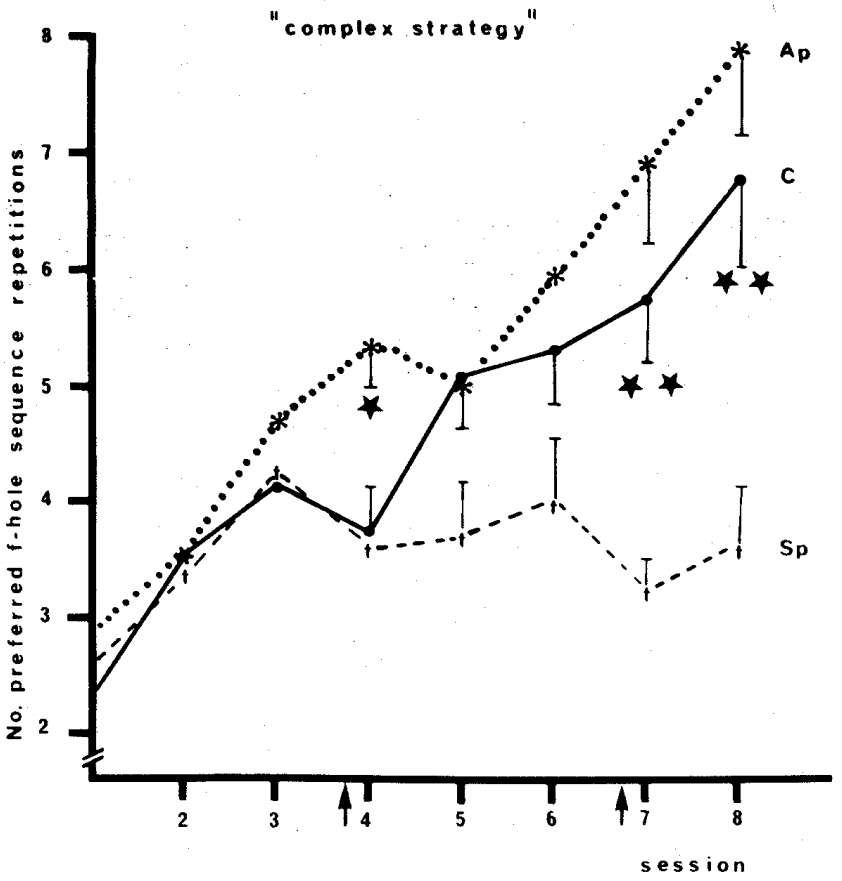

Fig. 3. The number of repetitions of the preferred food hole visit sequence per session (10 trials/session), across sessions, is shown for spiroperidol (Sp)-, apomorphine (Ap)- and vehicle-treated rats (C) on a hole-board search task. Injections into the VTA took place 15 min before sessions 4 and 7. While learning to find 4 food pellets consistently placed in 4 of 16 holes in the arena, animals of the C and Ap groups increased the frequency of repetitions of their preferred hole visit sequence over the 10 trials of each successive session. Spiroperidol treatment impaired this development. $^{\star}P < 0.05$; $^{\star\star}P < 0.01$.

TABLE I

CHANGES OF THE PREFERRED FOOD-HOLE VISIT SEQUENCE IN RATS

The proportion of sequence changes on sessions 4 and 7 describes the percentage of animals for which the preferred sequence on these sessions changed with respect to that shown on the previous session (n=number of animals in each experimental group). Frequency of sequence changes over 9 sessions describes the mean frequency of preferred sequence changes over the 8 inter-session intervals for all animals in each experimental group. Groups: VTA, lesion; Ap, apomorphine (intra-VTA); Sp, spiroperidol (intra-VTA); C, vehicle (intra-VTA). Statistics: $*P < 0.02$, $U = 32.5$, MW (2-tailed); $**P < 0.02$, $U = 26$, MW (2-tailed); $***0.02\ P < 0.05$, $U = 40$, MW (2-tailed).

Experimental group	Proportion of sequence changes on				Frequency of sequence changes over 9 sessions	
	Session 4		Session 7			
	n	Mean %	n	Mean %	Mean %	S.E.M.
C	14	50	14	43	51.8	± 5.0*,***
Ap	12	83	11	27	56.1	± 3.9**
Sp	12	75	9	78	76.5	± 5.0**,*
VTA	12	75	11	64	67.7	± 3.8***

The proportion of intersession preference changes across all sessions was also examined for the VTA lesion was a chronic condition. The same effect emerged and proved significant (Table I, right). Of particular interest is that the large number of animals that changed their preference on session 4 after apomorphine injection, is reduced to a far smaller proportion than in the control group on session 7 (Table I, left).

In conclusion the degree to which a normal rat visits a sequence of food-holes in a preferred order is reduced following VTA damage or injection of the dopamine antagonist spiroperidol into the VTA. Treatment of the VTA with apomorphine reduced, whereas spiroperidol or lesion treatment increased, the number of inter- and intra-sessional strategy (hole visit sequences) changes with respect to controls that were acquiring a preferred sequence of hole visits. It has been reported [1] that the application of butyrophenone neuroleptics to the VTA increased mesocortico-limbic neuronal activity. This could be the result of blocking dendritic autoreceptors or inhibition from short axon dopaminergic cells in the VTA. There is no known long axon innervation of the VTA from another dopaminergic cell group. Thus spiroperidol probably increases dopaminergic activity in the mesocorticolimbic pathway by blocking the inhibitory self-regulation exerted by the dendrites of dopaminergic cells in the VTA (disinhibition). VTA damage produced similar effects on these measures to spiroperidol treatment. This may be the result of an increase in the number of postsynaptic dopaminergic receptors in the mesocorti-colimbic projection areas resulting from denervation supersensitivity [3].

It is suggested that increased dopaminergic activity in mesocorticolimbic projections is responsible for switching central mechanisms controlling behavioural strategies. By contrast, reduced activity (e.g. apomorphine effect) reduces the frequency of switching behavioural strategy. This effect would facilitate the later stages of learning where animals have had some success in finding food. This interpretation receives support from investigations of the function of the VTA and its projection areas [2, 4–6, 8, 11]. This suggestion could prove important for the interpretation of the role of dopamine in frontal and limbic cortices.

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