Enhanced Suppression of a Conditioned Avoidance Response by Haloperidol but not Phenoxybenzamine in Rats with Bilateral Parafascicular Lesions

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Summary. Male rats were subject to bilateral lesions in the parafascicular nucleus (PF) of the thalamus. The lesions had little or no effect on the performance of a pre-operatively acquired conditioned avoidance response. However, the PF lesioned animals displayed an enhanced response to the dopamine receptor blocking agents haloperidol or pimozide but not to the noradrenaline receptor blocking agent phenoxybenzamine. The results indicate that intralaminar thalamic nuclei and dopaminergic extrapyramidal motor pathways are functionally connected.

Key words: Rat – Avoidance conditioning – Parafascicular nucleus – Dopamine – Noradrenaline

A number of studies have shown that medial thalamic lesions impair active avoidance in the rat and that lesions of the intralaminar nuclei are particularly effective (Vanderwolf 1962; Thompson 1963; Delacour 1971). That this effect of medial thalamic lesions is similar to the effects of the drug reserpine was noted by Thompson (1963). The suppression of conditioned avoidance behavior in the rat by reserpine as well as by a number of later developed antipsychotic agents is due to an impairment of central dopaminergic neurotransmission (e.g., Ahlenius 1979a).

The intralaminar nuclei are connected to the basal ganglia, where dopamine (DA) has an important role as a neurotransmitter (Carlsson 1972). Thus, in a number of species the parafascicular nucleus (PF), the nucleus centralis lateralis and the nucleus paracentralis project into the caudoputamen (Droogleever-Fortuyn 1950; Droogleever-Fortuyn and Stefens 1951; Nauta and Whitlock 1954; Powell and Cowan 1954; Cowan and Powell 1955; Jones and Leavitt 1974; Kuypers et al. 1974; Nauta et al. 1974) and these nuclei receive a projection from the substantia nigra, pars reticula (SNR) (Clavier et al. 1976; Ahlenius 1978, 1979b; Beckstead et al. 1979).

In support of a functional connection between the PF and DA pathways it was recently shown that catalepsy produced by the DA receptor blocking agent haloperidol (HPD) was enhanced by subtotal lesions of the PF (Ahlenius 1978). The present experiments were undertaken to investigate a possible functional connection between the PF and brain DA in the mediation of active avoidance conditioning in the rat.

Materials and Methods

Animals

Twenty-nine male Sprague-Dawley rats (Anticimex, Sollentuna, Sweden) were used. After arrival, the animals were allowed 1 week of adaptation before being used in an experiment. During the experiments the animals were housed individually and maintained on a restricted diet to keep their body weight at around 300 g throughout the experiments.

Drugs

Haloperidol (HPD), pimozide (PIM), and phenoxybenzamine (PBZ) (Leo, Helsingborg, Sweden) were used. HPD and PIM were dissolved in a few drops of glacial acetic acid and the final volume was made up with 5.5% glucose. PBZ was dissolved in a few drops of N HCl and 0.9% saline was added to the final volume. The drugs were injected i.p. in a volume of 2 ml/kg.

Surgery

The animals were deeply anesthetized with Equi-Thesin (Salisbury-Jensen, Kansas City, MO) and mounted in a stereotaxic...
apparatus (Stoelting Co., Chicago, IL). With reference to the stereotaxic atlas of König and Klippel (1963) bilateral radio-frequency heat lesions (LM4, Grass Instruments, Quincy, MA) were aimed at the parafascicular nucleus (PF) and some neighboring structures. The electrode was made of stainless steel (2.0.0.29 mm), insulated except for the wedge-formed tip (0.3 mm exposure of uncoated electrode). The general procedure was to keep the current at 10 mA until coagulation occurred, normally within 10 s.

**Conditioning Apparatus**

The animals were trained to perform a conditioned avoidance response (CAR) in a two-way shuttle box (540x220x250 mm, internal dimensions). The box was divided into two compartments by a partition with an opening 70 x 90 mm. The shuttle-box, made of transparent Plexiglas, was housed in an insulated ventilated enclosure and the animals were observed through a one-way mirror.

The conditioned stimulus (CS) was the sound of a house buzzer. The unconditioned stimulus (UCS) was an intermittent grid shock (50 Hz, 700 V), delivered through the grid floor of either compartment of the shuttle-box for 0.5 s every 2.0 s. The CS was presented alone for a maximum of 10 s. If no response occurred within 10 s, the CS was followed by CS plus UCS for a maximum of another 10 s. A large internal resistance (270 kΩ) diminished the influence of the resistance of the rat.

The duration of the shock and the interval between shocks were automatically timed but presentation of the CS and UCS was manually operated. The following behavioral items were recorded: (1) An avoidance response if the rat crossed the midline of the shuttle-box within 10 s of CS presentation; (2) an escape response if the animal crossed within 10 s of combined CS/UCS presentation; (3) an escape failure if the animals remained on the same side of the box for the entire 20 s trial; (4) the response latency; (5) the number of intertrial crosses.

The animals were given daily training sessions consisting of 20 trials within 15 min until they performed 85% avoidance in three consecutive sessions. Experimental sessions consisted of 10 trials distributed over 7.5 min.

**Experimental Procedure**

Following the acquisition of a CAR as described above, the animals were given pre-operative drug tests. During this time the animals were given one or more of the following treatments: (1) HPD, 0.0625 mg/kg; (2) PIM, 0.125 mg/kg; (3) PBZ, 10 mg/kg. These doses of the various drugs were found in separate experiments to produce no significant effects on the avoidance performance.

At least 2 days intervened between successive drug treatments. Following these pre-operative drug tests the animals were subject to brain lesions as described above. One week following surgery the animals were tested for the CAR performance and as needed given additional training sessions until pre-operative performance was obtained. The animals were thereafter observed in post-operative test sessions with the same treatments as given pre-operatively. When given more than one treatment the drugs were administered in a balanced order to the 4–6 animals that could be run on any given day pre-operatively. The order of drug administrations was reversed post-operatively.

Of 20 animals subject to lesions in the PF, six rats received HPD and PIM, 11 received HPD and PBZ or PIM and PBZ. Three animals received PIM only. The remaining nine animals were subject to control lesions in the habenula (4), ventro-lateral thalamus (1), medio-dorsal nucleus (2), the nuclei centraulis lateralis and paracentralis (3).

**Histology**

At the end of the experiments the animals were given an overdose of barbiturate and were perfused with 0.9% saline followed by a 10% formalin solution. The brains were immediately taken out and stored in 10% formalin. Three days before processing, the brains were transferred to a 15% sucrose/10% formalin solution. The brains were cut at 40 μm on a freezing microtome and the sections were collected in six compartments. Three compartments of the brain sections were mounted and stained with cresyl violet for determination of the center of the lesions within ±120 μm in each compartment. The level of the lesions was determined by reference to the atlas of König and Klippel (1963).

**Results**

The variation in the maximal destruction of the PF was from 0.00–2.28 mm. There was a significant correlation between the extent of the lesion in the PF and the avoidance suppression induced by sub-threshold doses of HPD or PIM (r = 0.59, p < 0.01), the smaller lesions causing no or minor suppression of avoidance. Since the material did not allow a determination of the minimum lesion required for interaction with HPD or PIM, each of the respective groups given the two drugs was arbitrarily divided in one sub-group with lesions larger than the median lesion size and one sub-group with lesions smaller than the median. The results are based on the respective sub-group with the larger lesion. There was no statistically significant difference between the pre- and post-operative performance (Table 1) in the nine animals thus included (Figs. 2 and 4).

### Table 1. Pre- and post-operative control performance of the rats described in Figs. 1–5. Shown are the grand medians (range) of the performance of nine rats in pre-drug control sessions (−10 min in Figs. 1 and 3). Statistical evaluation by means of Wilcoxon t-test

<table>
<thead>
<tr>
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<th>Avoidance (%)</th>
<th>Response latency (s)</th>
<th>Intertrial crosses (number)</th>
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<tbody>
<tr>
<td>PRE-OP.</td>
<td>100.0 (90.0–100.0)</td>
<td>1.4 (1.1–2.1)</td>
<td>0.0 (0.0–4.0)</td>
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<tr>
<td>POST-OP.</td>
<td>100.0 (80.0–100.0)</td>
<td>2.0 (1.2–3.0)</td>
<td>0.0 (0.0–6.0)</td>
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