Impaired response control in the rat after 6-hydroxydopamine lesions to the dorsal noradrenaline bundles

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The dorsal noradrenaline (NA) containing pathway in the rat brain arises from the locus coeruleus and innervates the limbic system and cortex. 6-Hydroxydopamine (6-OHDA) 8 μg dissolved in 2 μl of 0.9% sodium chloride solution containing 1 mg/ml of ascorbic acid when injected bilaterally into the dorsal NA bundle at a site anterior to the locus coeruleus results in virtually total and selective loss of NA from the limbic system and cortex.

Ten male albino Wistar rats were given such 6-OHDA lesions and one week later were compared with vehicle treated control animals on the acquisition of a running response for food reward in an L-maze. The 6-OHDA-lesioned animals achieved a stable running speed as quickly as control animals. However, when food was no longer presented in the goal box extinction of this learned running response proceeded more slowly in 6-OHDA-treated rats than in the controls (Trials to extinction, Mann Whitney U-Test $U = 2.0$, $P < 0.001$).

The animals were subsequently trained in a Skinner box to press a lever on a continuous schedule of food reinforcement; the 6-OHDA dorsal bundle lesioned animals were not impaired in learning this new response and after 10 days training were emitting equal numbers of lever presses. Food presentation was then stopped and it was found that during the first two days of extinction, the 6-OHDA-lesioned rats made more responses to the lever ($P < 0.05$) than the controls. Finally, acquisition of a successive visual discrimination in a Skinner box was studied in which the rats, after further training on the continuous food reinforcement schedule, were required to respond for food when the Skinner box houselight was on and to refrain from responding on trials when it was switched off. The dorsal bundle lesioned animals were slow to develop the discrimination habit as they failed to inhibit responses on the non-rewarded dark trials. During the first days of testing the 6-OHDA-lesioned animals consistently recorded more responses during the dark trials (ratio of light to dark lever presses $X^2 = 41.72$ d.f. $= 14$ $P < 0.001$ and overall responding on dark trials, $X^2 = 35.61$ d.f. $= 14$, $P < 0.01$).

At the end of the experiments the brains of 5 6-OHDA-treated and 5 control animals were assayed for forebrain noradrenaline and dopamine levels using a radio-enzymatic assay method. After the 6-OHDA treatment, noradrenaline levels in the hippocampus were reduced from 0.333 ± 0.069 ng/g to unmeasurable levels and in the cortex from 0.174 ± 0.068 ng/g to 0.001 ± 0.002 ng/g. Dopamine levels in the appropriate forebrain segments were unaffected.

This pattern of impairments in the dorsal bundle animals is characterized by difficulty in extinguishing responses in previously rewarded situations. Rats with surgical lesion to the hippocampus show similar deficits. It is suggested that the classical hippocampal syndrome in the rat can be mimicked to a large degree by selective loss of forebrain NA.

Dopamine and drug-induced hyperactivity in rats

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We have investigated the relations between on the one hand the concentration of dopamine (DA) and its deaminated metabolite dihydroxyphenylacetic acid (DOPAC) in the rat corpus striatum, and on the other the hyperactivity which follows the subcutaneous injection of dexamphetamine sulphate 1.18 mg/kg (DEX), chlordiazepoxide hydrochloride 12.5 mg/kg (CDZP) or a mixture of both these doses (MIX). It had previously been shown that the mixture produced in rats a high level of activity in a Y-maze which could not be elicited by any dose of either drug given separately (Rushton, Steinberg & Tomkiewicz, 1973).

Female hooded rats of about 200 g were killed 20, 40, 60 or 80 min after injection, the striata dissected out and DA and DOPAC levels measured by the methods of Laverty and Sharman (1965) and Murphy, Robinson & Sharman (1969) respectively. At the same times after injection the activity of other groups of rats was tested by placing animals individually in a Y-shaped maze

for 5 min, and recording the number of entries into the three arms.

The table shows that DEX raised DA and lowered DOPAC, the peak effects occurring at 40 min, which coincided with peak activity in the Y-maze. Changes in DA closely paralleled changes in activity. CDZP did not significantly alter DA or DOPAC but raised activity in the Y-maze, the peak effects occurring at twenty minutes. The mixture produced at all times more activity than either of the ingredient drugs, and this effect was relatively independent of the time after injection. Changes in DA and DOPAC were however rather similar to those produced by DEX, except that peak effects on DA occurred at sixty minutes.

Since the effects of the three treatments on DA and DOPAC were studied in separate experiments it is not possible to make strict comparisons between them. Nevertheless, the results suggest that the increased activity caused by DEX may be related to an effect on dopaminergic neurones in rat striatum. There is no indication that this is so for CDZP, and the time course of the effect of the mixture on DA and DOPAC bears no obvious relation to the persistently high level of activity induced by the mixture throughout the experiments.

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Table

		Minutes after injection				
		20	*40*	*60*	*80*	*Controls*
DEX	DA	115 ± 5	140 ± 2*	126 ± 7*	126 ± 7*	4.81 ± 0.29 μg/g (4)
	DOPAC	69 ± 9	66 ± 6*	68 ± 11	105 ± 21	1.09 ± 0.13 μg/g (4)
	Entries	143 ± 16*	215 ± 22*	171 ± 26*	192 ± 14*	++
CDZP	DA	111 ± 5	99 ± 5	99 ± 9	104 ± 9	5.41 ± 0.37 μg/g (4)
	DOPAC	97 ± 19	106 ± 10	112 ± 12	106 ± 20	1.20 ± 0.11 μg/g (5)
	Entries	195 ± 32*	179 ± 34*	164 ± 26*	122 ± 10	++
MIX	DA	113 ± 6	121 ± 7	135 ± 5*	124 ± 6*	5.45 ± 0.23 μg/g (4)
	DOPAC	64 ± 8*	60 ± 7*	60 ± 8*	67 ± 2*	1.09 ± 0.12 μg/g (4)
	Entries	251 ± 17*†	246 ± 15*	244 ± 15*†	256 ± 11*†	++

Values are expressed as percentages of control values and are the means ± s.e. mean of at least 5 animals. For DA and DOPAC the calculations are based on the control values from the same experiments only. The number of animals for these controls is shown after the concentration in the controls column.

++ The mean activity for all controls was 15.0 ± 0.7 entries in 5 minutes ($n = 6$).

Student's t tests: * $P < 0.05$ compared with controls.
† $P < 0.05$ compared with DEX.

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