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