Norepinephrine: Turnover in Rat Brains after Gonadectomy

Abstract. *The rate at which ^{3}H-norepinephrine disappears from rat brain increases after gonadectomy; the effect is observed 6 days after the operation and 24 hours after introduction of the labeled material; it is not reproduced by hypophysectomy. The content of endogenous brain norepinephrine does not decline after removal of the ovaries or testes; thus synthesis of the catecholamine is probably increased by these procedures.*

Considerable evidence indicates that brain catecholamines participate in the control of ovulation (*1, 2*). Moreover the concentrations of these neurotransmitters in brain are influenced by the level of gonad function (*2–4*). When male (*3*) or female rats (*2, 4*) are castrated, the norepinephrine content of the hypothalamus increases within 10 days. Drugs that deplete the hypothalamus of its norepinephrine appear to suppress the release of luteinizing hormone from the pituitary and to potentiate the secretion of prolactin (*5*). Our investigations demonstrate that the turnover of brain norepinephrine in rats increases after removal of the gonads.

Adult Sprague-Dawley male and female rats weighing 150 to 170 g were gonadectomized or sham-operated, maintained under normal lighting (lights on from 0600 to 1800 hours; 27 to 54 mphot at the level of the animals), and given Purina Chow and water ad libitum. Tritiated norepinephrine (*6*) was diluted with Ringer solution, and 6 μc (30 μl) was injected into the right lateral cerebral ventricle by a reported method (*7*). Earlier investigations had shown that, when ^{3}H-norepinephrine is introduced into the cerebrospinal fluid in this manner, it mixes bilaterally with the endogenous catecholamine (*7, 8*).

Animals were decapitated at intervals, the brains were removed, and the left halves were assayed for unchanged ^{3}H-norepinephrine (*9*). In all experiments the amount of labeled catecholamine in the injected side did not differ from that in the uninjected side. Endogenous brain norepinephrine was measured by the method of von Euler and Lishajko (*10*).

Oophorectomized and sham-operated rats were killed 1, 6, and 24 hours after receiving the tritiated amine intraventricularly. The concentrations of labeled norepinephrine did not differ significantly between treated and control groups after 1 and 6 hours, but, when death came 24 hours after injection, the level of ^{3}H-norepinephrine in brain was about two-thirds as high in oophorectomized as in control rats (9.2 $\pm$ 0.88 mμc/g versus 15.2 $\pm$ 2.02 mμc/g; $P < .001$). The effect was similar in male animals: brains of castrated rats contained 4.57 $\pm$ 0.67 mμc/g while those of control males contained 7.62 $\pm$ 0.85 mμc ($P < .01$). All subsequent experiments used animals killed 24 hours after injection.

To determine whether the effect of removal of the ovaries was immediate or required the passage of several days, the rate of turnover of brain ^{3}H-norepinephrine was studied in rats 2, 6, and 21 days after oophorectomy. Six days after surgery, retention of ^{3}H-norepinephrine by the brain 24 hours after its injection was only 54 percent of that observed in sham-operated animals ($P < .01$); the effect was similar at 21 days ($P < .001$) (Table 1).

Removal of the pituitary gland did not change turnover of brain ^{3}H-norepinephrine after 6 days: 24 hours after the amine was administered, its brain concentration was 13.1 $\pm$ 2.7 mμc/g in hypophysectomized female rats against 13.8 $\pm$ 1.6 mμc/g in sham-operated controls. The failure by hypophysectomy to simulate the effects of gonadectomy on turnover of ^{3}H-norepinephrine in the brain suggests that this latter effect really results from either (i) an action of pituitary gonadotrophins on the brain, or (ii) the total absence of gonadal hormones, which are still produced in small amounts in hypophysectomized animals.

Table 1. Development of increased turnover of ^{3}H-norepinephrine (^{3}H-n) in brains of oophorectomized rats. Rats were killed 24 hours after ^{3}H-norepinephrine was injected into the right lateral ventricle. The left side of the brain was assayed for the labeled catecholamine.

Days after surgery	Brain ^{3}H-n, exp.:control (%)
Control	100 $\pm$ 11.5
2	83 $\pm$ 3.0
6	54 $\pm$ 11.1*
21	60 $\pm$ 4.9*

*Differs from that of control rats; $P < .01$.

In all our studies the total norepinephrine content of the brain was increased by about 15 percent 20 days after gonadectomy, but these increases were not always statistically significant. Since brain norepinephrine content did not decline after removal of the gonads, the increase in turnover of ^{3}H-norepinephrine in the brain indicates that more of the amine must have been synthesized per unit time in castrated animals. Experiments in which norepinephrine synthesis was inhibited pharmacologically (*2*) have led to similar conclusions. The increase in turnover must also be associated with a steady-state rise in the rate at which brain norepinephrine is released or metabolized. Preliminary studies indicate that the activity of the metabolizing enzyme monoamine oxidase is not altered in brains of castrated rats.

These observations demonstrate that the pituitary-gonadal axis regulates the rates at which brain norepinephrine is synthesized and turns over in the rat. They also strongly suggest that norepinephrine participates in the central regulation of gonad function in this species. The rise in turnover of ^{3}H-norepinephrine in the brain that follows gonadectomy is highly reproducible and should provide a useful model for study of brain-gonad relations.

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