(cf. Ref. 12, equation IV-2). This gives a linear Scatchard plot with no decrease in B_{max}. We are left, therefore, with no obvious model for reversible noncompetitive binding inhibition.

If we ignore this theoretical problem, and simply assume that B_{max} has two components, B_1 and B_2, the first being somehow noncompetitively inhibited by fluphenazine (5–100 nM), we have

$$B_{max} = B_1/(1 + [I]/K_i) + B_2$$

where $[I]$ is the concentration of fluphenazine and K_i its inhibitor constant. Fitting this to the data on B_{max} (Fig. 1) by using a least-squares curve fitting computer program, we obtain $B_1 = 64\%$ of B_{max} and $K_i = 18$ nM. This value of the fluphenazine-receptor dissociation constant agrees with reported estimates of the IC_{50} of the fluphenazine-induced inhibition of [^{3}H]spiroperidol binding to D-2 receptors [1]. It is, therefore, possible that fluphenazine regulates the high-affinity binding site of [^{3}H]DA allosterically through an interaction with the site labeled by ^{3}H neuroleptics.

In summary, our results suggest strongly that fluphenazine inhibits the major portion of the specific binding of [^{3}H]DA to its high-affinity receptors in rat striatum via a noncompetitive mechanism. Because there is no evident theoretical model for reversible noncompetitive binding inhibition, this interpretation must be approached with caution. Insofar as a similar mechanism was described for the morphine-induced displacement of [^{3}H]leucine enkephalin [14], the noncompetitive inhibition of neurotransmitter-receptor binding by antagonists may merit further investigation.

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Effect of ACTH on ornithine decarboxylase activity of adrenal medulla and cortex

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ACTH administration stimulates the induction of ornithine decarboxylase (ODC, EC 4.1.1.17) activity in the adrenal gland of experimental animals [1–3]. Thus far, there are results only for whole adrenal glands, and the effect of the hormone on the separate tissues making up the adrenal has not been determined. Our previous studies of the mechanisms of induction of adrenomedullary and -cortical ODC have indicated that for the chromaffin tissue the increase of activity caused by various stressors and drugs is mediated largely by neural mechanisms involving intact splanchnic innervation of the gland [4, 5] whereas the increase in adrenal cortex under the same conditions is mediated to an important extent by a hormonal component (*ibidem*). It is clearly important to establish the relation of induction by ACTH to the increases in ODC engendered by stressing animals. The effect of ACTH on ODC activity of the two separate tissues has now been studied.

Hypophysectomized male Sprague–Dawley rats, weighing about 200 g, were purchased from Canadian Breeding Farms and Laboratories Ltd., St. Constant, Quebec. They were kept in the animal room in individual wire cages under a light–dark cycle of 12:12 hr, with tap water and Purina Checkers *ad lib*. Five days after hypophysectomy, the rats received one subcutaneous injection of synthetic ACTH (10 I.U., equivalent to 0.1 mg/rat). Four to six animals were killed every 2 hr up to 12 hr, along with two additional groups at 18 hr and 24 hr after receiving ACTH. Adrenal medulla and cortex were separated at 4° by dissection under a magnifying lamp as previously described [4, 6]. The tissue corresponding to two medullae or two cortices was pooled and homogenized in 200 μl of Na^+–K^+–phosphate buffer, 0.05 M, pH 6.8, with a motor-driven Teflon homogenizer. The homogenate was centrifuged at 20,000 *g* for 20 min, and the supernatant fraction was taken for assay of ODC activity [4].

Sham-operated rats were used as controls in some experiments. They received 0.1 ml of a solution of 1% methylcellulose, instead of the ACTH solution. Otherwise their treatment was the same as above.

The results with hypophysectomized rats are shown in Fig. 1. Adrenomedullary ODC did not respond to ACTH administration in the time-course studied. On the other

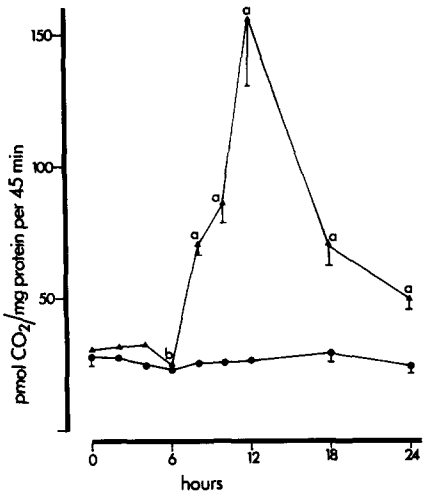

Fig. 1. Time-course of stimulation of adrenomedullary (●) and adrenocortical (▲) ODC following subcutaneous administration of 10 I.U. of ACTH. Each point represents the mean response of four to six hypophysectomized animals. Key: (a) $P < 0.001$, and (b) $P < 0.05$, for comparison of indicated mean with control.

hand, the cortical enzyme showed a significant increase at 6 hr, rising to a peak at 12 hr. Twenty-four hours after the administration of ACTH, the cortical enzyme still showed higher values than the controls.

The ODC activity in adrenals of hypophysectomized rats was compared with that in adrenals of sham-operated controls. The data in Table 1 show that basal medullary ODC activity was not altered by hypophysectomy. Cortical ODC, however, was significantly lowered as compared to these sham-operated controls. Other data in the table demonstrate the effect of two different doses of ACTH: 10 and 20 I.U. There was a slightly higher mean value with 20 I.U., but this was not significantly different from that obtained with 10 I.U. These results agree with the reports of Levine *et al.* [1, 2] who estimated that 10 I.U. of ACTH provide a maximal effect for induction of adrenal ODC.

A number of drugs and stressors [4–6] are capable of inducing ODC activity in both adrenal medulla and cortex. The present results exclude any obligatory role for ACTH in the induction of adrenomedullary ODC by such stimuli. On the other hand, this hormone could be expected to play an important role in the induction of adrenocortical ODC under the influence of stress or certain drugs. Indeed, the increase of adrenomedullary ODC activity caused by apomorphine, an effective inducer [7], is attenuated in hypophysectomized rats, but the increase of the cortical enzyme is completely abolished [6]. Thus, nervous pathways mediating the stress-induced increase of adrenocortical ODC can be expected to have their terminus in the hypothalamus, endocrine mechanisms taking over from that site onwards.

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Table 1. Effect of hypophysectomy and ACTH on adrenomedullary and -cortical ODC activity

Treatment	ACTH	Medulla	Cortex
Sham-operation		28 ± 2.3	61 ± 5.1† (6)
Hypophysectomy		27 ± 1.7	30 ± 1.1 (9)
Hypophysectomy	10 I.U.	26 ± 1.8	157 ± 25.3† (6)
Hypophysectomy	20 I.U.	28 ± 1.5	193 ± 52.3† (3)

* Values are means ± S.E.M. (number of animals in parentheses). Five days after surgery, the rats were injected with control solution and 10 or 20 I.U. ACTH. Animals were killed 12 hr later.

† $P < 0.001$, for comparison of indicated mean with hypophysectomized controls.