1. Owren, P. A., Acta Med. Scand., Suppl. **194**, 1 (1947).

2. Quick, A. J., Lancet **2**, 379 (1947).

3. Ware, A. G. and Seegers, W. H., J. Biol. Chem. **172**, 699 (1948).

4. Wright, I. S., Thromb. Diath. Haemorrhag. **3**, 435 (1959).

5. Ferguson, J. H., Hematologic Rev. in press.

6. Ferguson, J. H., Hematologic Rev. **1**, 69 (1968).

7. Quick, A. J. and Stefanini, M., J. Lab. Clin. Med. **33**, 819 (1948).

8. White, N. B., Ferguson, J. H., and Hitsumoto, S., Am. J. Med. Sci. **255**, 143 (1968).

9. Yin, E. T. and Wessler, S., J. Biol. Chem. **243**, 112 (1968).

10. Kerwin, D. M. and Milstone, J. H., Thromb. Diath. Haemorrhag. **17**, 247 (1967).

11. Ferguson, J. H., Ennis, E. G. (W.), Iatridis, P. G., and White, N. B., Thromb. Diath. Haemorrhag. **18**, 647 (1967).

12. Ferguson, J. H., Federation Proc. **23**, 762 (1964).

13. Ferguson, J. H., Thromb. Diath. Haemorrhag., Suppl. **4**, 226 (1960).

14. Lewis, M. L. and Ware, A. G., Proc. Soc. Exptl. Biol. Med. **84**, 640 (1953).

15. Ferguson, J. H., Marcus, A. J., and Robinson, A. J., Blood **22**, 19 (1963).

16. Esnouf, M. P. and Macfarlane, R. G., Advan. Enzymol. **30**, 255 (1968).

17. Surgenor, D. M., Wilson, N. A., and Henry, A. S., Thromb. Diath Haemorrhag. **5**, 1 (1960).

18. Prentice, C. R. M., Ratnoff, O. D., and Breckenridge, R. T., Brit. J. Haematol. **13**, 898 (1967).

19. Newcomb, T. F. and Yoshida, M., Scand. J. Clin. Lab. Invest., Suppl. **17**, (84), 61 (1965).

20. Ferguson, J. H. and Ennis, E. G. (W.), Proc. Soc. Exptl. Biol. Med. **130**, 486 (1969).

Received Sept. 4, 1968. P.S.E.B.M., 1969, Vol. 130.

The Effect of Exogenous Dopamine on ACTH Secretion (33575)

ALLEN B. KING[1]
(Introduced by W F. Ganong)
The Creighton University School of Medicine, Department of Medicine, Omaha, Nebraska 68131

Exogenous dopamine has been shown to increase corticotropin (ACTH) secretion as measured by adrenal ascorbic acid depletion (1). Since a dichotomy has been demonstrated between adrenal ascorbic acid depletion and plasma corticosterone elevation in some conditions (2, 3), the effect of dopamine on plasma corticosterone levels was determined.

Epinephrine, closely related in biological action and chemical structure to dopamine, is thought to raise ACTH blood levels by acting as a nonspecific peripheral stress (4). Therefore, dopamine and epinephrine in equivalent ACTH-stimulating doses were compared in their effect on blood pressure as a measurement of peripheral stress.

Dexamethasone inhibits the nervous pathways of corticotropin releasing factor (CRF) release (5). Since dopamine is thought to influence these same pathways (1), the influence of pretreatment with dexamethasone on the ACTH-raising ability of dopamine was studied.

Methods. Male albino rats (Holtzman Company) weighing about 200 g were used in all experiments. Animals received food and water *ad libitum*, and were housed in individual cages under a constant illumination schedule (7 a.m. to 7 p.m.) for more than 6 days. All experiments were carried out between 10 a.m. to 12 noon. The substance to be tested was injected s.c. in a volume of 0.2 ml 15 min before a plasma sample was obtained from the unanesthetized rats. Plasma samples were obtained by rapid decapitation, collection of the blood in heparinized tubes, and then aspiration of the plasma after centrifugation. The plasma samples were frozen until used. A solution containing ascorbic

[1] Present address: University of Colorado Medical Center, Department of Medicine, 4200 E. Ninth Ave., Denver, Colorado 80220.

acid (0.2 mg/ml) and EDTA (0.05 mg/ml) in distilled water was used to make the dopamine and epinephrine solutions and also was used for the control injections. Dexamethasone (25 μg/100 g) was given i.p. 2 hr before injection of the substance to be tested.

Corticosterone plasma levels were determined by minor modifications of the assay developed by Mattingly (6). All results were expressed in μg/100 ml of plasma.

Blood pressures were obtained from the carotid artery of rats anesthetized with both pentobarbital (4.5 mg/100 g) and ether. An average of the systolic and diastolic pressure was recorded just prior to the subcutaneous injection of the variable and 1 min after injection. Results were expressed in percentage increase in average blood pressure over preinjected levels. The significance of the results was tested by the t test and significance was defined as $p \leq 0.05$.

TABLE I. The Effect of Dopamine on Plasma Corticosterone.

Dopamine dose (μg/100 g)	No. of rats	Corticosterone (μg/100 ml)
Control	8	18.7 ± 1.0[a]
10	6	19.8 ± 2.5
100	9	28.6 ± 2.5[b]
1000	8	39.5 ± 4.0[b]

[a] Mean ± SEM.
[b] Statistically higher than control group ($p \leq 0.05$).

Results. Table I reveals that dopamine in doses of 10 μg/100 g was without effect while doses of 100 μg and higher produced a significant rise in plasma corticosterone. In a previous study dopamine was found to be effective in depleting adrenal ascorbic acid at a concentration of 10 μg/100 g (1).

Table II demonstrates that epinephrine (50 μg/100 g) and dopamine (100 μg/100 g) produced an equivalent rise in plasma corticosterone. In these same doses, epinephrine has a significantly greater effect on blood pressure.

Table III shows dexamethasone, given 2 hr prior to sacrifice, was able to cause a significant lowering of the control plasma corticosterone levels. Other workers (7) have shown

TABLE II. Comparison of the Effect of Dopamine and Epinephrine on Plasma Corticosterone and Average Blood Pressure (ABP).

Doses (μg/100 g)	No. of rats	Plasma corticosterone (μg/100 ml)	Percentage change in ABP in first min
Control	8	18.7 ± 1.0[a]	—
Epinephrine 50	5	27.7 ± 3.4[b]	30 ± 12[c]
Dopamine 100	9	28.6 ± 2.5[b]	3 ± 3

[a] Mean ± SEM.
[b] Statistically higher than control group ($p \leq 0.05$).
[c] Statistically higher than dopamine group ($p \leq 0.05$).

complete blockade of corticosterone rise associated with peripheral stress using the same dexamethasone protocol. Although pretreatment with dexamethasone was associated with a lowering of plasma corticosterone in both dopamine injected animal groups, both 100 and 1000 μg/100 g produced a significantly greater effect than control.

Discussion. These studies reveal that dopamine is capable of increasing ACTH secretion as indicated by plasma corticosterone elevation. It is also apparent that the adrenal ascorbic acid depletion method is as specific as the plasma corticosterone rise for measur-

TABLE III. The Effect of Dexamethasone Pretreatment on Plasma Corticosterone Elevation Following Dopamine Injection.

Dopamine (μg/100 g)	Dexamethasone dose (μg/100 g of body wt.)	No. of rats	Plasma corticosterone (μg/100 ml)
—	25	8	15.5 ± 1.0[a]
Control	—	8	18.7 ± 1.0[b]
100	—	9	28.6 ± 2.5[b]
100	25	6	18.8 ± 1.1[b,c]
1000	—	8	39.5 ± 4.0[b]
1000	25	6	31.6 ± 2.6[b]

[a] Mean ± SEM.
[b] Statistically higher than dexamethasone control group ($p \leq 0.05$).
[c] Statistically lower than same dose of dopamine alone ($p \leq 0.05$).

ing ACTH stimulation induced by dopamine (1).

As implied in a previous communication (1) and demonstrated in this work, dopamine appears to be able to stimulate ACTH secretion without causing a significant peripheral effect on blood pressure. On the other hand, epinephrine stimulates corticotropin secretion but also produces a significant elevation in blood pressure. This would agree with current thinking (8) that the plasma corticosterone rise associated with injected epinephrine is mediated through its peripheral actions.

The site at which dexamethasone and corticosterone act in diminishing CRF secretion is not known. Present evidence indicates that the site of inhibition is in the hypothalamus and midbrain areas (5). Since dopamine's action was not completely blocked by dexamethasone, part of dopamine's effect could be occurring beyond dexamethasone blockade. The possibility of dopamine causing enough peripheral stimulation to overcome dexamethasone inhibition can not be ruled out as an alternative explanation.

Recent work (9) has shown that reserpine implanatation into the median eminence depletes monoamine stores yet produces no change in ACTH rise in response to stress. This appears to deny dopamine a role in ACTH secretion. Despite depletion by reserpine of catecholamine stores, there remains a small functionally important catecholamine pool that maintains the function of the dopamine neurons in response to stress in spite of reserpine's action. Further work is needed to confirm dopamine's role as a regulator of ACTH secretion.

Summary. Dopamine in a dose which does not cause a significant rise in arterial blood pressure causes a significant increase in peripheral blood corticosterone. Dexamethasone partially suppresses this dopamine induced rise in corticosterone.

1. King, A. B. and Thomas, J. A., J. Parmacol. Exptl. Therap. **159**, 18 (1968).

2. Slusher, M. A., Endocrinology **63**, 412 (1958).

3. Slusher, M. A. and Critchlow, V., Proc. Soc. Exptl. Biol. Med. **101**, 497 (1959).

4. Ganong, W. F., *in* "Advances in Neuroendocrinology" (A. V. Nalbanov, ed.), p. 92. Univ. of Illinois Press, Urbana, Illinois (1963).

5. Mangili, G., Motta, M., and Martini, L., *in* "Neuroendocrinology" (L. Martini and W. F. Ganong, eds.), Vol. 1, p. 322. Academic Press, New York (1966).

6. Mattingly, D., J. Clin. Pathol. **15**, 374 (1962).

7. Hedge, G. A., Yates, M. B., Marcus, R., and Yates, F. E., Endocrinology **79**, 328 (1966).

8. Smelik, P. G., Neuroendocrinology **2**, 247 (1967).

9. Dahlström, A., Fuxe, K., Hamberger, B., and Hökfelt, T., J. Pharm. Pharmacol. **19**, 345 (1967).

Received Sept. 4, 1968. P.S.E.B.M., 1969, Vol. 130.