THE OCCURRENCE, DISTRIBUTION AND PHYSIOLOGICAL ROLE OF CATECHOLAMINES IN THE NERVOUS SYSTEM

ARVID CARLSSON

Department of Pharmacology, University of Lund, Lund, Sweden

In mammalian brain noradrenaline and dopamine are present in roughly equal quantities (Table 1).[1] Adrenaline occurs in much smaller amounts, much less than 10% of the noradrenaline, according to our results. In amphibian brain, on the other hand, as in other amphibian tissues, adrenaline appears to be predominant. Our data do not permit any definite conclusions concerning the presence of dopamine in amphibian brain.

In mammalian brain the distributions of dopamine and noradrenaline are markedly different. Practically all of the dopamine occurs in the corpus striatum, where high levels are found, whereas noradrenaline is present in highest concentration in the brain stem, notably the hypothalamus. A typical example, showing the distribution in the dog brain, is shown in Table 2.

The distribution of dopamine in tissues other than brain varies according to the species (Table 3). In certain tissues of ruminants (ox, sheep and goat), particularly the lungs and duodenum, high levels are found. These data confirm and extend some earlier observations by Goodall (12) and by von Euler and Lishajko (9). The occurrence of dopamine in ruminant tissues other than brain appears to coincide with the presence of a hitherto unknown type of chromaffin cells, according to investigations performed in cooperation with Hillarp and co-workers at the University of Lund. In other species (cat, dog, rabbit, guinea pig and rat) dopamine appears to present in appreciable amounts only in brain, and no chromaffin cells of this particular type have been found.

The markedly different distributions of dopamine and noradrenaline in brain as well as in peripheral tissues suggest that the function of dopamine is not merely that of a precursor of noradrenaline (3).

The administration of reserpine (1 mg per kg body weight intravenously) to rabbits causes the almost complete disappearance of both dopamine and noradrenaline from the brain (7). The effect is prevented largely by pretreatment with iproniazid (100 mg per kg by vein 6 hours prior to the injection of reserpine). The usual prevention by iproniazid of the tranquillizing action of reserpine was observed in these experiments.

Injection of dopa (3,4-dihydroxyphenylalanine; 150 mg per kg of the DL form intravenously) to normal and reserpinized rabbits causes a marked increase in the level of dopamine in brain (Table 4). The noradrenaline level is not much affected by dopa given alone. Pretreatment with iproniazid increases the effect of dopa on the dopamine level, and now there is a significant increase also in the noradrenaline level, although the effect on dopamine is much more pronounced.

[1] The data shown in this paper are taken from theses being prepared in our laboratory by Å. Bertler and E. Rosengren.

TABLE 1

Occurrence of adrenaline, noradrenaline, and dopamine in the brains of different species of animals

	Adrenaline	Noradrenaline	Dopamine
	μg/g	μg/g	μg/g
Sheep	—	0.25	0.30
Pig	—	0.14	0.22
Dog	—	0.16	0.19
Cat	—	0.16	0.22
Rabbit	—	0.22	0.28
Guinea pig	—	0.38	0.34
Rat	—	0.49	0.60
Frog and toad	1.4	0.26	—

TABLE 2

Distribution of noradrenaline and dopamine in the dog brain

	Noradrenaline	Dopamine
	μg/g	μg/g
Cerebral hemispheres (not corpus striatum, hippocampus)		
rostral part	0.13	0.07
caudal part	0.12	0.08
Caudate nucleus	0.10	5.90
Lentiform nucleus	0.08	1.63
Hippocampus	0.14	0.13
Hypothalamus	0.76	0.26
Diencephalon (not hypothalamus)	0.17	0.09
Mesencephalon	0.33	0.20
Pons	0.41	0.10
Medulla oblongata	0.37	0.13
Cerebellum	0.06	0.03

The experiments with dopa reported here indicate that this amino acid can penetrate into brain. In fact, we have found very high levels of dopa in the brains of rabbits injected with this amino acid. After entering brain, the dopa is apparently decarboxylated to form dopamine. L-dopa decarboxylase is known to be present in brain (13). The fact that both the accumulation of catecholamines in brain and the central excitation caused by dopa are strongly potentiated by iproniazid, indicates that the central excitation is not produced by dopa as such but by the amines formed from it.

Some of the actions of reserpine appear to be related to the loss of catecholamines. First of all, as shown by us in 1956 (2, 8) and later by Muscholl and Vogt (15, 16), the adrenergic nerves cease to function under the influence of reserpine, owing to lack of their transmitter substance. This conclusion later received additional support through the demonstration by chemical methods, that the release of catecholamines into blood following stimulation of the ad-

TABLE 3

*Noradrenaline (NA) and dopamine (DA) in mammalian tissues**

	Heart		Lung		Spleen		Liver		Kidney		Duodenum		Sympathetic trunk		Sciatic nerve	
	NA	DA	NA	DA	NA	DA	NA	DA	NA	DA	NA	DA	NA	DA	NA	DA
Cow	1.0	1.5	0.1	9.5	1.0	0.8	0.1	2.5	0.2	0.2	—	—	—	—	—	—
Sheep	1.0	0.3	0.1	6.9	1.9	0.9	0.2	.0.3	0.0	0.0	—	—	—	—	—	—
Goat	1.4	0.5	0.1	5.3	6.8	1.0	0.1	1.6	0.7	2.0	0.2	6.3	1.2	0.6	0.1	0.4
Pig	—	—	0.1	0.0	—	—	—	—	—	—	—	—	—	—	—	—
Dog	1.0	0.0	0.1	0.0	1.1	0.0	0.3	0.0	1.3	0.0	—	—	1.8	0.1	—	—
Cat	1.2	0.0	0.3	0.0	2.9	0.1	0.1	0.0	0.1	0.0	0.5	0.2	—	—	—	—
Rabbit	1.4	0.0	0.0	0.2	—	—	0.1	0.0	0.2	0.0	0.4	0.2	—	—	—	—
Guinea pig	2.6	0.0	0.2	—	—	0.4	0.2	0.0	0.6	0.0	—	—	—	—	—	—
Rat	0.8	0.0	0.1	0.0	0.6	0.1	0.1	0.0	0.1	0.0	—	—	—	—	—	—

* All figures are given in μg/g.

TABLE 4

Effect of dopa, reserpine-dopa, and reserpine-iproniazid-dopa on the catecholamine content of rabbit brain

	Noradrenaline	Dopamine
	μg/g	μg/g
Controls (4 animals)	0.22	0.28
Dopa	0.36, 0.41	0.89, 0.75
Reserpine + dopa	0.05, 0.03	0.85, 0.34
Reserpine + iproniazid + dopa	0.19, 0.12	5.7, 3.7

The drugs were given intravenously. Doses: DL-dopa 150 mg/kg; reserpine 1 mg/kg; iproniazid 100 mg/kg. Intervals: reserpine 16 hr; iproniazid 8 hr; dopa 0.3 hr before killing the animals.

renergic nerves no longer occurs after treatment with reserpine (1). It is tempting to look upon the adrenergic nerves as a relatively simple model system, which illustrates the way in which reserpine interferes with nerve function.

There is some evidence to show that the depressant action of reserpine on motor activity is at least partly due to lack of catecholamines: this action of reserpine can be efficiently antagonized by injection of dopa (6). 5-Hydroxytryptophan, which is the precursor of 5-hydroxytryptamine (17), is inefficient in this respect. On the other hand, centrally acting sympathomimetic amines, notably desoxyephedrine, are also efficient in restoring to normal the motor activity of reserpinized animals, as shown by Everett and co-workers (10). Presumably these drugs are capable of serving as substitutes for the catecholamines. Injected catecholamines, on the other hand, are inefficient as reserpine antagonists, presumably because they do not easily penetrate into brain.

The corpus striatum forms an important part of the extrapyramidal system, which is known to control motor activity (4). Lesions in this system are ac-

companied by different kinds of kinetic disorder. Thus the Parkinsonian syndrome is characterized by slowing and enfeeblement of emotional and voluntary movement, muscular rigidity, and tremor. Chorea, on the other hand, presents features which are in some respects the opposite of the symptoms of Parkinsonism, with involuntary movements and, frequently, emotional instability. It is interesting to note that reserpine, which depletes the dopamine from the corpus striatum, may produce a syndrome very similar to Parkinsonism and appears to be efficient in controlling the choreatic syndrome (5, 11, 15).

Thus the following facts argue for the assumption that dopamine is involved in the control of motor functions.

1) The presence of large amounts of dopamine in the corpus striatum, which forms an important part of the extrapyramidal system.

2) The extrapyramidal actions of reserpine, which depletes the dopamine from the corpus striatum.

3) The ability of dopa to counteract the hypokinetic action of reserpine. Whether this action of dopa is entirely due to formation of dopamine, or whether formation of noradrenaline contributes to the effect, remains an open question.

REFERENCES

1. Bertler, Å., Carlsson, A., Lindqvist, M. and Magnusson, T.: On the catechol amine levels in blood plasma after stimulation of the sympathoadrenal system. Experientia **14**: 184, 1958.
2. Bertler, Å., Carlsson, A. and Rosengren, E.: Release by reserpine of catechol amines from rabbits' hearts. Naturwissenschaften **43**: 521, 1956.
3. Blaschko, H.: Metabolism of mediator substances. In: Psychotropic drugs, ed. by S. Garattini and V. Ghetti, pp. 3-9. Elsevier, Amsterdam, 1957.
4. Brain, R.: Diseases of the nervous system, 4th ed. Oxford Univ. Press, London, 1951.
5. Brander, E.: Über die Beeinflussung extrapyramidaler Motilitätsstörungen mit neuroplegisch wirksamen Pharmaka (Reserpin, Chlorpromazin). Mschr. Psychiat. Neurol. **132**: 81-95, 1956.
6. Carlsson, A., Lindqvist, M. and Magnusson, T.: 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature, Lond. **180**: 1200, 1957.
7. Carlsson, A., Lindqvist, M., Magnusson, T. and Waldeck, B.: On the presence of 3-hydroxytyramine in brain. Science **127**: 471, 1958.
8. Carlsson, A., Rosengren, E., Bertler, Å. and Nilsson, J.: Effect of reserpine on the metabolism of catechol amines. In: Psychotropic drugs, ed. by S. Garattini and V. Ghetti, pp. 363-372. Elsevier, Amsterdam, 1957.
9. Euler, U. S. von and Lishajko, F.: Dopamine in mammalian lung and spleen. Acta physiol. pharm. néerl. **6**: 295-303, 1957.
10. Everett, G. M., Toman, J. E. P. and Smith, A. H., Jr.: Central and peripheral effects of reserpine and 11-desmethoxyreserpine (harmonyl) on the nervous system. Fed. Proc. **16**: 1263, 1957.
11. Gerstenbrand, F. and Weingarten, K.: Serpasil-Behandlung bei extrapyramidalen Hyperkinesien. Wien. klin. Wschr. **68**: 656-659, 1956.
12. Goodall, McC.: Studies of adrenaline and noradrenaline in mammalian heart and suprarenals. Acta physiol. scand. **24**: suppl. 185, 42-46, 1951.
13. Holtz, P. and Westermann, E.: Über die Dopadecarboxylase und Histidindecarboxylase des Nervengewebes. Arch. exp. Path. Pharmak. **227**: 538-546, 1956.
14. Kirkpatrick, W. L. and Sanders, F.: Clinical evaluation of reserpine in a state hospital. Ann. N. Y. Acad. Sci. **61**: 123-143, 1955.
15. Muscholl, E. and Vogt, M.: The action of reserpine on sympathetic ganglia. J. Physiol. **136**: 7P-8P, 1957.
16. Muscholl, E. and Vogt, M.: The action of reserpine on the peripheral sympathetic system. J. Physiol. **141**: 132-155, 1958.
17. Udenfriend, S., Weissbach, H. and Bogdanski, D. F.: Increase in tissue serotonin following administration of its precursor 5-hydroxytryptophan. J. biol. Chem. **224**: 803-810, 1957.