Studies on the action of guanethidine on the central nervous system and on the norepinephrine content of the brain

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In recent communications the pharmacological properties of a new hypotensive agent, guanethidine ((2-)octa-hydro-1-azocinyl)-ethyl)-guanidine sulphate) are described, including protracted blockade of carotis occlusion pressor responses and potentiation of norepinephrine.[1, 2] It was suggested that the compound might interfere with release[3] and/or normal distribution[4] subsequent to release of neurohormonal transmitter at the sympathetic neuromuscular junctions. The action of guanethidine is similar to some extent to the action of reserpine.[5]

The present paper shows that the drug produces some effect on the central nervous system and decreases the level of norepinephrine in the brain.

The effect on the motility was investigated on white mice with the motimeter of Knoll.[6] Table 1 represents the effect of 5 mg/kg guanethidine administered s.c. 3 hr before the experiments on

Table 1. Motility of white mice
(The number represents the motimeter count during 30 min.)

	Drug	mg/kg	Number of animals	Counts motimeter	Significance
I.	—	—	70	216	
II.	Guanethidine	5	25	268	I–II $P > 0.5$
III.	Amphetamine	5	25	979	I–III $P < 0.01$
IV.	Guanethidine	5	25	419	III–IV $P < 0.01$
	Amphetamine	5			

Table 2. Norepinephrine (NE) levels of rat brain ng/g wet tissue

Hour	Number of animals	NE (ng/g)	Per cent decrease	Significance
0	15	307 ± 56		
1	9	161 ± 36	48	$P < 0.01$
3	15	123 ± 38	60	$P < 0.01$
6	10	220 ± 36	22	$P < 0.01$
24	10	221 ± 36	22	$P < 0.01$
48	6	267 ± 43		
72	4	304 ± 17		

spontaneous motility and on hypermotility brought about by 5 mg/kg s.c. Amphetamine. The spontaneous motility does not change, whereas the Amphetamine hypermotility decreases by more than 50 per cent.

The estimation of the norepinephrine (NE) in the brain was made on white rats after administration of 5 mg/kg s.c. guanethidine. The animals were decapitated in such a way that head fell into liquid air. The extraction was made according to the method of Euler[7] and the estimation of NE was carried out biologically, using blood pressure of cats according to Paasonen and Krayer.[8] Guanethidine significantly decreases the level of NE in the brain. After 1 hr the effect already appears and the maximal effect is manifest after 3 hr, when the level of NE is decreased by 60 per cent. The effect is visible even after 24 hr and full restoration takes place only after 48–72 hr (Table 2).

According to the investigation of Cass *et al.*[3] guanethidine depletes the NE in heart and spleen of rabbits and cats without lowering NE in the brain. The cause of the contradiction in the aforesaid and present data may be due to the species difference. According to the above-mentioned authors the drug probably cannot penetrate the brain owing to its low solubility in lipoid. The present result, however, namely that it inhibits the effect of Amphetamine, indicates its penetration into the central nervous system.

The Pharmacological Institute,
The Medical School,
Budapest, Hungary.

A. KLÁRA PFEIFER
E. SZ. VIZI
ÉVA SÁTORY

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Separation of a transplantation antigen

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TRANSPLANTATION antigens have successively been assumed to be: deoxyribonucleoproteins,[1] mucopolysaccharides of the blood groups type,[2] and glycoproteins.[3] The controversy is due to the fact that the antigens have never been purified. The main hindrance to the purification of those substances has been the time-consuming test for antigenicity (*in vivo* test).[1] Recent work[4, 5] raised the possibility of detecting transplantation antigens by a serological method (*in vitro* test). Hereafter, *in vivo* activity will be referred to as sensitizing activity and *in vitro* activity as serological activity. As the identity of the agents in both tests has yet to be confirmed, the main fractions studied here have been checked for their sensitizing as well as for their serological activity.

Mice of the inbred strains A/Jax (H-2^a), C57BL/6J (H-2^b), CBA (H-2^k) and ASW (H-2^s) were used.

Extraction. Antigens have been extracted from spleen and thymus cells as previously described.[3] The insoluble residue after lyophilization was made up of proteins, lipids and carbohydrates. Its serological and sensitizing activity was high.

Solubilization. A very mild acid hydrolysis (HCl, pH 2, 50 °C, 4 hr) led to part of the residue being solubilized. Centrifugation (100,000 g, 1 hr) provided a supernatant which exhibited a high serological activity and a poor sensitizing activity. It was soluble in water and contained proteins, polypeptides, lipids and carbohydrates, among which free sialic acid.

Fractionation. The supernatant was separated by dialysis against distilled water (48 hr, Visking cellulose casing 8/32) into a serologically inactive dialysable fraction, and a serologically highly active non-dialysable fraction. The latter was obtained in the form of a very hygroscopic white powder (dry weight, 0·01 per cent of the wet weight of fresh organs) giving a perfectly clear solution in water and

* Details will be published elsewhere.