

EFFECT OF CENTRAL NEUROTROPIC SUBSTANCES ON PERIODIC  
CONTRACTIONS OF THE DOG'S STOMACH WHEN INJECTED  
INTO VARIOUS ARTERIES OF THE BRAIN

(UDC 612.327-06:615.78-032:611.133.33]-084)

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Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 58, No. 11,  
pp. 63-66, November, 1964

Original article submitted July 4, 1963

Investigations by Soviet workers have shown that morphine, apomorphine, and hexonium, in small doses, have a stimulating effect on the periodic contractions of the dog's stomach, while methyldiazil\*, hexobarbital, chlorpromazine, and adrenalin inhibit them. Although, pharmacologically, most of these substances are centrally acting, since many of their properties are associated with a direct action on the central nervous system, the central mechanism of their action on the motor activity of the stomach has not been proved. It is known that besides their central action, these substances also have a peripheral action.

The object of the present investigation was to determine the mechanism of action of these substances on the periodic contractions of the stomach, and if this mechanism is central, at what level of the central nervous system this action takes place in each individual case. It was proposed to obtain this information by means of experiments in which the substances were injected into various arteries of the brain and intravenously, followed by comparison of the doses required to obtain a minimal effect by each method of administration.

#### METHOD

For drugs stimulating motor activity the minimal effect from the action of the substances on the periodic contractions of the dog's stomach was the appearance of an ectopic period of contractions, while for drugs inhibiting motor activity it was the cessation of gastric contractions for a period of between 3 and 5 min. To increase the individual variability of the doses of the tested drugs, they were compared mainly in the same animal, and then verified in experiments on another.

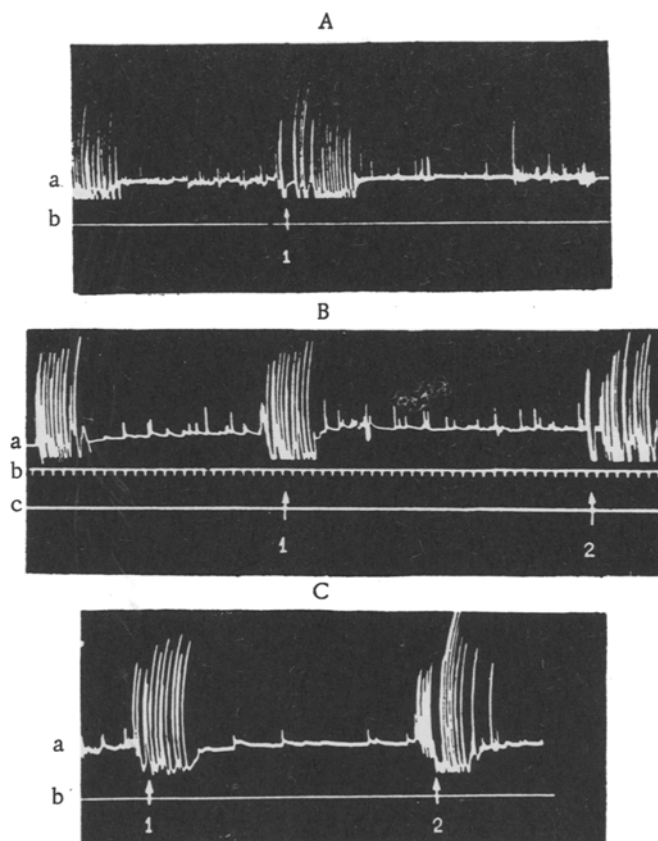
Altogether 168 experiments, lasting many hours, were conducted on 7 dogs, in the course of which 380 observations were made following injection of the drugs into different arteries. In order to inject the drugs into the brain-stem structures, the vertebral artery was used: a polyethylene catheter was inserted into this vessel by a special technique [1]. Injection of the drugs into parts of the brain situated above the brain stem was carried out through the internal carotid artery. For this purpose the drugs were injected into the common carotid artery, all the branches of which, with the exception of the internal carotid artery, were ligated. The gastric contractions were recorded on the kymograph by means of a hydro-pneumatic system, through a gastric fistula.

#### RESULTS

The intravenous injection of morphine (0.06 mg/kg) or apomorphine (0.02 mg/kg) into the dogs led to the appearance of a period of ectopic contractions. However, injection of these drugs in the same doses into the brain stem through the vertebral artery was not followed by the appearance of ectopic contractions, but by depression of the periodic activity of the stomach. The inhibitory effect was evidently brought about by the fact that these doses

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\*Methyl derivative of diazil, Russian equivalent of benactyzine hydrochloride.



Effect of hexobarbital on contractions of the dog's stomach depending on the method of injection and the dose. A) After intravenous injection in a dose of 8 mg/kg (1); B) after intravenous injection in a dose of 0.8 mg/kg (1) and injection into the vertebral artery in a dose of 0.8 mg/kg (2); C) after injection into the internal carotid artery in a dose of 1 mg/kg (1) and 2 mg/kg (2); a) gastric contractions; b) marker of injection of drugs; c) time marker (4 min).

of the drugs were excessive for injection into the brain stem, and they evoked a pessimal reaction (depression) of the centers. This became obvious after the determination of the minimal doses of these substances causing ectopic contractions of the stomach when injected into the vertebral artery. These proved to be only one-fifteenth the doses for intravenous injection: for morphine—0.004  $\mu$ g/kg, for apomorphine—0.001 mg/kg. The intravenous injection of these doses of morphine and apomorphine produced no motor reaction of the stomach. To produce gastric contractions by injection of these drugs into the internal carotid artery the minimally active doses were somewhat increased: for morphine—to 0.009 mg/kg and for apomorphine—to 0.005 mg/kg. Hence, the central action of morphine and apomorphine on the motor activity of the stomach was associated with high sensitivity of the structures of the brain stem to these drugs.

Methyldiazil (metamysil), when injected intravenously, produced a minimal inhibitory effect in respect of gastric contractions during the working period in a dose of 0.05 mg/kg. The same effect was produced by injection of this substance into the vertebral artery in a dose of 0.005 mg/kg, and by injection into the internal carotid artery in a dose of 0.02 mg/kg. A brief period of arrest of the gastric contractions was produced by intravenous injection of hexobarbital in a dose of 8 mg/kg, by injection of this drug into the internal carotid artery in a dose of 2 mg/kg, and by injection into the vertebral artery in a dose of 0.8 mg/kg (see figure).

In contrast to the two preceding drugs, chlorpromazine produced the most marked inhibitory effect when injected into the brain above the brain stem. The minimally active dose, when injected into the internal carotid artery, was 0.05 mg/kg, when injected into the vertebral artery—0.2 mg/kg, and when injected intravenously—1.3 mg/kg.

Minimal Doses of Neurotropic Substances (in mg/kg) Acting on the Motor Activity of the Stomach, when Injected into Different Arteries of the Brain

Substance	Mode of injection			Level of action
	Intravenously	Into internal carotid artery	Into vertebral artery	
Morphine	0.06	0.009	0.002	Brain stem
Apomorphine	0.02	0.005	0.001	" "
Methyldiazil	0.05	0.02	0.005	" "
Hexobarbital	8.0	2.0	0.8	" "
Chlorpromazine	1.3	0.05	0.2	Above brain stem
Hexamethonium	0.05	0.05	0.05	Periphery
Adrenalin	0.005	0.005	0.005	"

The injection of hexamethonium intravenously and into the various arteries of the brain in identical doses produced the same effect—ectopic contractions of the stomach. The minimal dose for obtaining this effect by whatever method of injection was 0.06 mg/kg. The intravenous injection of adrenalin (0.005 mg/kg) during periodic contractions produced a temporary arrest of the contractions lasting 5-6 min. Injection of this substance in the same dose into any artery of the brain produced an effect of exactly the same strength and duration.

On the basis of the results obtained, the neurotropic drugs investigated may be divided into two main groups by their mechanism of action: centrally and peripherally acting. The former include substances influencing the motor function of the stomach when injected into the arteries of the brain in a dose too small to produce an effect when injected intravenously. Conversely, substances producing the same effect in minimal doses regardless of the method of injection are predominantly peripheral in their action. In this way two drugs—adrenalin and hexamethonium—having a peripheral action on gastric motor activity may be distinguished.

Although the method which was used did not enable a distinction to be made between the reflex peripheral action of the agents investigated and their local action on the neuromuscular apparatus of the stomach, we assume that the stimulating action of small doses of hexamethonium is associated with its nicotine-like cholinomimetic effect on the synapses of the gastric nerve plexuses, and that of adrenalin with its direct relaxant action on smooth muscle. The remaining drugs were 8-15 times more active when injected into the arteries of the brain than when injected intravenously, thereby demonstrating the central character of their action.

Nevertheless, a difference may be noted between these substances also, as regards their central action. Some of them act most strongly and in smaller doses when injected into the vertebral artery, while others behave in this way when injected into the internal carotid (see table). These drugs evidently act at different points in the central nervous system when modifying gastric contractions: morphine, apomorphine, methyldiazil, and hexobarbital act mainly through the brain stem, while chlorpromazine acts on parts of the brain lying above the brain stem.

The facts described provide further evidence to show that the regulation of gastric contractions is effected through the participation of different divisions of the central nervous system.

#### LITERATURE CITED

1. V. E. Ryzhenkov, L. L. Grechishkin, and G. A. Artamonov, *Farmakol. i toksikol.*, 3 (1962), p. 282.