10679

Effects of Anesthetics on the Response of Submaxillary and Pancreatic Glands to Prostigmine and Physostigmine.

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In an analysis of the nervous secretory mechanism of a gland it is appropriate to use drugs which may excite or depress nerve endings. In this investigation prostigmine and physostigmine were selected. Prostigmine was selected because its effect on pancreatic secretion and its relative effect on pancreatic and salivary secretion has not been determined. Physostigmine was selected because, although it is known to stimulate pancreatic[1, 3] and salivary[2] secretion, the relative action of the drug on the pancreatic and salivary glands has not been determined in the same animal. It was also desired to ascertain whether as the dosage of the drug was increased a "reversal" in the secretory response of the gland occurred, as had been shown to occur in the case of the action of acetyl-beta-methyl choline on the gastric glands.[4]

Dogs were anesthetized with either sodium pentobarbital (30 mg per kilo), chloralose (French, 100 mg per kilo), or paraldehyde (1.8 cc per kilo). The latter 2 anesthetics were employed because the former may have a pseudo-atropine action on the vagus.[5]

The pancreatic and submaxillary ducts were cannulated. A blood pressure record was made to ascertain the simultaneous effects of the drugs on the circulatory system. The pyloric sphincter was occluded to prevent the gastric secretion from entering the intestine. The drugs were injected intravenously. *Prostigmine* was given in doses ranging from 0.005 to 0.2 mg per kilo; *physostigmine* in doses ranging from 0.01 to 0.2 mg per kilo. The drugs were injected either at 30- or 60-minute intervals. A control secretion was always obtained and a basal flow was awaited before a second injection of a drug was made.

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1 Crittenden, P. J., and Ivy, A. C., *Am. J. Physiol.*, 1937, **118**, 724.

2 Loewi, O., and Mansfield, G., *Arch. f. exp. Path. u. Pharmakol.*, 1909-10, **62**, 180.

3 Babkin, B. P., Herb, C. O., and Sergeyev, M. A., *Am. J. Physiol.*, 1938, **123**, 5.

4 Gray, J. S., and Ivy, A. C., *Am. J. Physiol.*, 1937, **120**, 705.

5 Linegar, C. R., Dille, J. M., and Koppanyi, T., *J. Pharm. and Exp. Therap.*, 1936, **58**, 128.

Pancreatic Secretion: Pentobarbital anesthesia. The following observations pertain to the results obtained on 11 animals. *Prostigmine* stimulated pancreatic secretion in all animals. The threshold dose was 0.005 mg per kilo. The maximal secretory response, which on the average amounted to 35 drops or 1.7 cc was obtained with 0.06 mg per kilo. Larger doses produced less and less secretion, so that with a dose of 0.2 mg per kilo only 17 drops or 0.8 cc of juice were obtained. *Physostigmine* stimulated pancreatic secretion. The threshold dose was 0.01 mg per kilo and the maximum secretory response was obtained usually with 0.2 mg per kilo, the average maximal output of secretion being 30.5 drops or 1.5 cc. A reversal of the response with larger doses could not be clearly established because larger doses were frequently fatal.

These results show that the pancreas is more sensitive to *prostigmine* than *physostigmine* and that a "reversal" of the secretory response may occur with large doses of prostigmine.

When the injections were made at one-hour intervals the results were the same, with the exception that they showed that the action of *prostigmine* on the pancreas lasted somewhat longer than 30 minutes.

Salivary Secretion: Pentobarbital anesthesia. The threshold dose of *prostigmine* was about 0.01 mg per kilo. The maximal secretory response occurred with a dose of 0.1 mg per kilo and average 7.5 cc in amount. With larger doses a "reversal" in the secretory response occurred as in the case of the pancreas. The threshold dose of *physostigmine* was about 0.03 mg per kilo and the maximal secretory response, average 1.3 cc, was obtained with 0.2 mg per kilo.

Thus, the submaxillary gland responds to *prostigmine* and *physostigmine* similarly to the pancreas, with the exception that the submaxillary gland produces a greater volume of secretion. The dosage differences are not due to differences in molecular concentration of the drugs.

Chloralose and paraldehyde anesthesia. Five animals were anesthetized with chloralose and 4 with paraldehyde. Both of these anesthetics raised the threshold dose and decreased the volume output of secretion in the case of each drug. More experiments were not performed with these anesthetics because their deleterious effects were obvious. For example, with chloralose anesthesia the maximal secretory response to *prostigmine* averaged only 3.6 cc instead of 7.5 cc under pentobarbital.

With equivalent doses, *prostigmine* had a greater effect on blood pressure (increases, as a rule) and heart rate (slows) regardless of

the anesthesia used, than *physostigmine.* This observation is contrary to that made by Aeschilmann and Reinert[6] on the frog and rabbit, but it supports the use of belladonna and its alkaloids when large doses of *prostigmine* are given in myasthenia gravis.[7] The effects of *physostigmine* on blood pressure were more variable than those of *prostigmine,* but agree with the effects reported by Heathcote[8] in that small doses usually cause a rise and large doses a fall. The effect of *prostigmine* on the heart rate of chloralosed dogs was most striking. With a dose of 0.05 mg per kilo and above, the pulse was markedly slowed and the pulse pressure was greatly increased, measuring from 70 to 90 mm Hg.

Only one point of interest will be discussed and that is in reference to the mechanism of the *prostigmine reversal,* which is of interest in relation to observations made previously on the response of the pancreas and stomach to acetyl choline.[1, 3, 4] Chloralose affected the cardiac mechanism so that *prostigmine* caused a very large pulse pressure which indicated vagal stimulation. Chloralose also markedly decreased the response of the glands to *prostigmine.* This suggests that the "reversal" noted with pentobarbital anesthesia was due to a selective stimulation of the excitatory and inhibitory mechanisms of the gland, the larger doses affecting the inhibitory mechanism chiefly. Chloralose probably stimulated or sensitized the inhibitory mechanism of the gland and then *prostigmine* produced less secretion than when pentobarbital was the anesthetic. Koppanyi[5]

TABLE I.
Average Effect of Pancreatic Secretion in Drops.

Dose in mg per kilo		0.01	0.02	0.05	0.06	0.075	0.1	0.2
Prostigmine								
Pentobarbital	30′	2	9.5	22	35	19	17	12
"	60′		7.5	17		16.5	14	
Paraldehyde			0.0	2		7	18	
Chloralose		0.5	2	2.5		8	5	2
Physostigmine								
Pentobarbital	30′	0.5	1.6	7		7	12.5	30
"	60′			6		10	12	
Paraldehyde				2		1	4	
Chloralose				2		0.0	1.5	

This table shows (in drops) the average effects of various doses of *prostigmine* and *physostigmine* on pancreatic secretions in animals anesthetized with either sodium pentobarbital, paraldehyde, or chloralose. The "reversal" of effect on the secretion is marked following *prostigmine* when the animals are anesthetized with sodium pentobarbital and the drug injected at thirty-minute intervals.

[6] Aeschilmann, J. A., and Reinert, M., *J. Pharm. and Exp. Therap.,* 1931, **43,** 413.

[7] Walker, M. B., *Proc. Roy. Soc. Med.,* 1935, **28,** 759.

[8] Heathcote, R. St. A., *J. Pharm. and Exp. Therap.,* 1932, **44,** 95.

has presented evidence indicating that pentobarbital has an atropine-like action in the cardiac vagal mechanism. If it has a similar effect on the "parasympathetic" or vagal inhibitory mechanism of the pancreas (or submaxillary), then pentobarbital would favor *prostigmine* stimulation of secretion and also *physostigmine* stimulation, which it does; and, on the basis that chloralose has the opposite action (*i. e.*, to pentobarbital) on the inhibitory mechanism, less secretion would be obtained with both *prostigmine* and *physostigmine,* which was observed. The observed effects of paraldehyde, however, do not agree with the foregoing hypothesis because paraldehyde affected the secretory response to *prostigmine* and *physostigmine* like chloralose, but not the cardiac response, although the degree of cardiac slowing was similar.

Summary and Conclusions. *Prostigmine* and *physostigmine* were administered intravenously in doses ranging from 0.005 mg to 0.2 mg per kilo to dogs anesthetized with either sodium pentobarbital, chloralose, or paraldehyde. The effects on pancreatic and salivary secretion and on the blood pressure and heart rate were recorded.

1. In the lower doses *prostigmine* is a more potent excitant of pancreatic and submaxillary secretion than *physostigmine.* A "reversal" in the response of the pancreas occurred when the dose of *prostigmine* was increased above 0.06 mg per kilo, and of the submaxillary gland in doses above 0.1 mg per kilo.

2. Chloralose anesthesia markedly diminishes the secretory response of the pancreas and submaxillary secretion to *prostigmine* and *physostigmine;* the same is true of paraldehyde anesthesia.

10680

Determination of Vitamin C Nutrition by Means of a Skin Test. A Critical Evaluation.

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Rotter[1, 2] suggested that the state of vitamin C nutrition could be determined by means of a skin test in which 0.01 cc of a 1/400

[1] Rotter, H., *Nature,* 1937, **139**, 717.
[2] Rotter, H., *Klin. Wchnschr.,* 1938, **51**, 205.