the activity of the omasal wall was greatly augmented and became continuous. The rhythmic activity of the omasal leaves was slightly altered, the discharge becoming a little (about 20%) more frequent. The possible contribution of a response to abomasal acid secretion was eliminated by showing that injection of 50 ml of 0.1 *N* HCl into the omasal canal caused only a slight and passing electrical response.

The electrical activity of the omasum was related to pressure changes in the cattle. In the bull, electrical activity of the greater curvature of the omasal wall was recorded by means of chronically implanted electrodes; and in the cow the activity of the leaves was detected by use of a balloon bearing several silver electrodes which was inflated within the omasum. These records showed that pentagastrin greatly increased the activity of the wall but only slightly affected the leaves, as with the sheep, and that the increased electrical activity paralleled the increase in omasal pressure.

This pattern of effects, inhibition of rumino-reticulum and stimulation of the omasum, was not shown by other smooth muscle stimulants. Rapid i.v. injection of hypertensin 2 µg/kg, or serotonin, 20 µg/kg, stimulated the electrical activity of the musculature of all compartments of the stomach, as did pilocarpine, 100 µg/kg, and carbachol, 4 µg/kg. Adrenaline, 2 µg/kg, after a brief stimulating effect, inhibited all compartments. Secretin, 1 IU/kg, and pancreozymin, 2 IU/kg, had no effect. The injection of atropine, 200 µg/kg, arrested all pressure changes and electrical activity; injection of pentagastrin, 2 µg/kg, about 6 min later, always produced an omasal response that was not much less than normal.

These effects of pentagastrin on the smooth muscle of the forestomach appear specific and quite unusual, for 1. unlike other smooth muscle excitants or cholinomimetic drugs with a nicotinic action, excitation of the omasum was accompanied by cessation of rumino-reticular activity, and 2. unlike parasympathomimetic effects, the contraction of the omasum could be produced after atropinization of the organ. The specific excitation of the omasum accords well with its origin from the central part of the lesser curvature of the embryonic gastric spindle[5], since this is the region which is most responsive to pentagastrin in monogastric species[2].

Résumé. L'injection i.v. de 6 µg/kg de gastrine synthétique (ICI 50123) est suivie, chez les herbivores ruminants, malgré une inhibition prolongée de la motricité rumino-réticulaire, d'une importante contraction de l'omasum (feuillet). La réponse excito-motrice persiste après atropine et semble spécifique du feuillet qui équivaut, sur le plan embryologique, à la partie moyenne de la petite courbure de l'estomac.

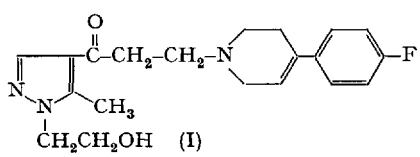
Y. RUCKEBUSCH

Laboratoire de Physiologie et Pharmacodynamie, École Nationale Vétérinaire, F-31 Toulouse (France), 23 October 1970.

[5] R. S. COMLINE, I. A. SILVER and D. H. STEVEN, *Handbook of Physiology*, Section 6: Alimentary Canal (American Physiological Society, Washington 1968), chapter 125.

Antihypertensive Agents III. Synthesis and Antihypertensive Activity of 3-[4-(*p*-Fluoro-phenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-[1-(2-hydroxyethyl)-5-methyl-4-pyrazolyl]-1-propanone[1-3]

CIBA 4416/B-Go, which is 3-[4-(*p*-fluorophenyl)-1, 2, 3, 6-tetrahydro-1-pyridyl]-1-[1-(2-hydroxyethyl)-5-methyl-4-pyrazolyl]-1-propanone citrate (I), has been studied to ascertain its antihypertensive properties in experimental animals.



(I)

Go 4416 is a potent hypotensive agent in experimental animals. It produces a prolonged fall of blood pressure of 40–50 mm Hg lasting for about 2 h at a dose of 0.25 mg/kg, when given i.v. or intra-intestinally in pentobarbitone-anaesthetized dogs and cats. At this dose the adrenaline effect is either reversed or blocked. The noradrenaline effect is slightly reduced. The substance inhibits the carotoid occlusion pressor response and antagonizes the pressor response elicited by tyramine and amphetamine.

This compound affects central vasomotor regulating mechanisms as evidenced by the production of prolonged fall of blood pressure after intra-arterial injection into vertebral artery of anaesthetized cats (10–20 µg/kg).

Go 4416 lowers significantly the blood pressure of renal hypertensive rats (−21 to −82) at a dose of 5–30 mg/kg p.o. when given daily for 10 days. The compound has no ganglion-blocking activity, as evidenced by similar diminution of contraction of the nictitating membrane of the cat following pre- and post-ganglionic cervical sympathetic stimulation. The diminished contraction of the nictitating membrane (43% at 1 mg/kg i.v.) following Go 4416 could be attributed to α-adrenoreceptor block. This compound does not block transmission in the adrenergic neurons, as demonstrated in the Finkelman preparation.

Go 4416 produces a significant depletion of heart (39%) and brain (55%) noradrenaline at 10 and 30 mg/kg respectively. Brain dopamine and 5-hydroxy-tryptamine are also significantly lowered (about 50%) with the higher dose.

The compound produces marked peripheral vasodilation. This has been shown on the isolated perfused hind limb of a cat and on femoral blood flow in the anaesthetized dog. The blood flow is increased by 64 and 120% with 50 and 100 µg/kg i.v. respectively, as measured by an electromagnetic flow meter.

A convenient method of preparation of Go 4416B is as follows: Ethoxymethylene acetylacetone is reacted

[1] Citrate = CIBA 4416/B-Go.

[2] Previous paper: V. P. ARYA, R. S. GREWAL, C. L. KAUL, S. P. GHATE, D. V. MEHTA and T. GEORGE, J. Pharm. Sci. *58*, 432 (1969).

[3] Contribution No. 243 from CIBA Research Centre.

with 2-hydroxyethyl hydrazine to give 4-acetyl-1-(2-hydroxyethyl)-5-methyl-pyrazole, m.p. 138°; calculated for $C_8H_{12}N_2O_2$. C, 57.13; H, 7.19; N, 16.66%. Found: C, 57.32; H, 7.32; N, 16.42%; UV: λ_{max}^{ETOH} 246 nm (log ε 4.05); IR (nujol): 1658 cm^{-1}, 3290 cm^{-1}. Mannich condensation of the above pyrazole with 4-(*p*-fluorophenyl)-1, 2, 3, 6-tetrahydro pyridine hydrochloride and paraformaldehyde in the presence of catalytic amounts of hydrochloric acid affords the hydrochloride from which the base is liberated. The base (I), m.p. 148°, calculated for $C_{20}H_{24}FN_3O_2$; C, 67.20; H, 6.77; N, 11.76. Found: C, 67.38; H, 6.93; N, 11.64; UV: λ_{max}^{ETOH} 248 nm (log ε 4.39); IR (nujol): 1670 cm^{-1}. On treatment with citric acid in methanolic solution, the base forms the citrate, m.p. 136°, calculated for $C_{26}H_{32}FN_3O_9$; C, 56.82; H, 5.87; N, 7.65. Found: C, 56.86; H, 6.07; N, 7.47. UV: λ_{max}^{ETOH} 248 nm (log ε 4.41).

Zusammenfassung. 3-[4-(*p*-Fluorphenyl)-1, 2, 3, 6-te-trahydro-1-pyridyl]-1-[1-(2-hydroxyaethyl)-5-methyl-4-pyrazolyl]-1-propanon (I, CIBA 4416/B-Go) senkt bei normotonischen und hypertonischen Tieren den Blutdruck. Die Drucksenkung kann hauptsächlich auf die periphere Vasodilatation sowie auf die Vasomotorenzentren bezogen werden. Ausserdem wirkt CIBA 4416/B-Go adrenolytisch.

V. P. Arya, R. S. Grewal,
C. L. Kaul and S. P. Ghate

CIBA Research Centre, Goregaon East, Bombay 63 (India), 1 April 1971.

Antagonism of Dibutyryl-Guo-3′:5′-P and Atropine on Stomach Smooth Muscle Contraction

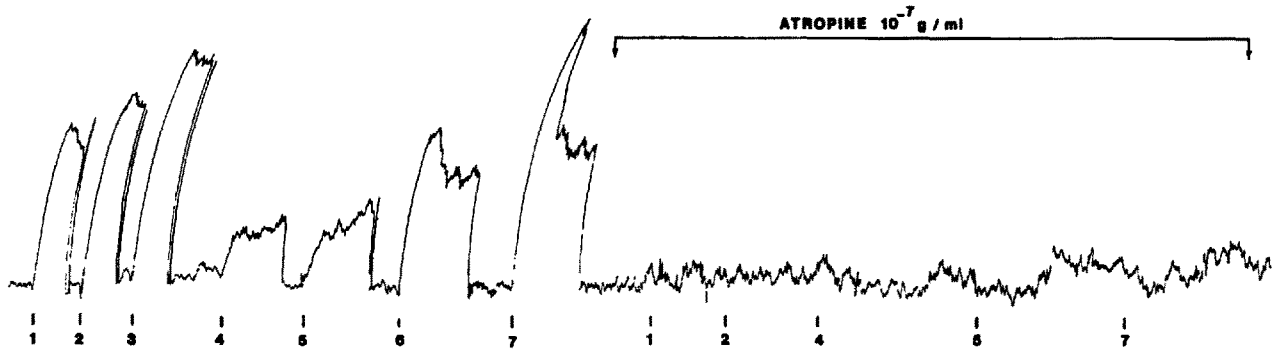
The effects of cyclic-adenosine-3′5′-monophosphate (Ado-3′:5′-P) and its dibutyryl derivative (db-Ado-3′:5′-P) on smooth muscle activity are well known[1-3]. Furthermore, basal and stimulated motility of the stomach in the dog, as well as in man, is reduced or abolished during db-Ado-3′:5′-P infusion[4], while blood perfusion pressure is unaffected. Smooth muscle relaxation can be associated with increased concentrations of Ado-3′:5′-P, induced by catecholamines through activation of β-receptors[5]. The α-receptor effects of catecholamines, however, could be mediated by a decrease of the intracellular Ado-3′:5′-P levels which in turn determines smooth muscle contraction[6]. Ball et al.[7] were able to demonstrate that α-adrenergic agents increase, in man, the extracellular cyclic-guanosine-3′5′-monophosphate (Guo-3′:5′-P). Also, it has recently been shown that, at least under some conditions, Guo-3′:5′-P activates the phosphodiesterase enzyme system responsible for the inactivation of Ado-3′:5′-P[8].

Cyclic-3′5′-guanosine-monophosphate is present in considerable amounts in various mammalian tissues, particularly in the gastrointestinal tract[9] and is affected by hormones and other factors, in a different way to Ado-3′:5′-P[10].

These findings and the results obtained by Manganiello et al.[11] in adipose tissue, where Ado-3′:5′-P and Guo-3′:5′-P act in opposite directions, prompted us to investigate the effect of the compounds on the gastric smooth muscles. The experiments were carried out on the rat stomach fundus strip prepared according to Vane[12].

Our results demonstrate that, also in this tissue, the 2 cyclic nucleotides act in opposite directions. While db-Ado-3′:5′-P antagonizes the effect of acetylcholine

[1] E. W. Sutherland, I. Øye and R. W. Butcher, Rec. Prog. Horm. Res. *21*, 623 (1965).
[2] E. W. Sutherland, G. A. Robison and R. W. Butcher, Circulation *27*, 279 (1968).
[3] G. A. Robison, R. W. Butcher and E. W. Sutherland, A. Rev. Biochem. *37*, 149 (1968).
[4] R. A. Levine, E. P. Cafferata and E. F. McNally, Proc. 3rd World Congress of Gastroenterology, Tokyo, 1967, vol. 1, p. 408.
[5] E. Bueding, R. W. Butcher and J. Hawkins, Biochim. biophys. Acta *115*, 173 (1966).
[6] G. A. Robison, R. W. Butcher and E. W. Sutherland, Ann. N.Y. Acad. Sci. *139*, 703 (1967).
[7] J. H. Ball, N. I. Kaminsky and A. E. Broadus, Clin. Res. *18*, 336 (1970).
[8] J. A. Beavo, J. G. Hardman, E. W. Sutherland, J. biol. Chem., in press (1971).
[9] E. Ishikawa, S. Ishikawa, J. W. Davis and E. W. Sutherland, J. biol. Chem. *244*, 6354 (1969).
[10] J. G. Hardman, J. W. Davis and E. W. Sutherland, J. biol. Chem. *244*, 6371 (1969).
[11] V. Manganiello, F. Murad and M. Vaughan, Fedn Proc. *28*, 876 (1969).
[12] J. R. Vane, Br. J. Pharmac. *12*, 344 (1957).



Effect of atropine sulfate on the action of acetylcholine-HCl (Ach) and dibutyryl-cyclic-3′,5′-guanosine monophosphate (db-Guo-3′:5′-P) on the isolated rat stomach fundus strip. 1, Ach, 4 µg/ml; 2, Ach, 6 µg/ml; 3, Ach, 8 µg/ml; 4, db-Guo-3′:5′-P, 125 µg/ml; 5, db-Guo-3′:5′-P, 250 µg/ml; 6, db-Guo-3′:5′-P, 375 µg/ml; 7, db-Guo-3′:5′-P, 500 µg/ml. Perfusion with Tyrode solution; bath volume 10 ml; temperature 37 °C. Atropine sulfate 1×10^{-7} g/ml was added to the tyrode solution for 60 min, after which, in its presence responses 1, 2, 4, 5 and 7 were repeated.