Gastric Secretory Response of Shay Rats to ICI-50123

The synthetic gastrin-like pentapeptide ICI-50123 (butyl-oxycarbonyl-β-ala.try.met.asp.phe.amide) is commonly employed in gastric secretory studies. Doses producing a maximal stimulation of gastric acidity have been reported to be 6 μg/kg in man[1], 80 μg/kg in the cat[2], 40 μg/kg in the dog[3] and 512 μg/kg in the Ghosh and Schild perfused rat stomach[4]. Data for the pylorus-ligated Shay rat are not available, yet this preparation is still frequently used in the testing of anti-ulcer compounds[5]. Reported here are dose response curves for gastric juice volume, volume/100 g, acidity, total acidity, acid output and gastric juice pH following graded doses of ICI-50123. The 2 h rather than the 4 h pylorus-ligated preparation was used[6,7].

Male Sprague-Dawley rats weighing 297.1 ± 6.3 g from the Charles River Laboratories (Charles River Laboratories, Wilmington, Mass.) breeding shed 1 were used. Animals were housed in colony cages under controlled environmental conditions (temperature, 68 °F, light, 17.00–07.00) and fed Purina rat chow (Ralston Purina Co., St. Louis, Mo.). 24 h prior to study the rats were weighed and then isolated from food only in a monkey cage with a 1 inch square mesh floor to reduce coprophagy: water was supplied ad libitum. The isolation weight was used to calculate drug dose. After the 24 h fast the rats weighed 261.7 ± 6.2 g. Under open ether anesthesia the pylorus was ligated with silk through an upper abdominal mid-line incision. After closure, the skin wound was painted with collodion. The anesthesia and operation required 2–4 min. Recovery had usually occurred within a further 5 min. Following surgery the rats were randomly divided into 8 groups (10–20 rats/group) and injected s.c. with either ICI-50123 or drug vehicle solution (1.0 ml/kg). Doses of ICI-50123 were 100.0, 300.0, 400.0, 800.0, 1000.0, 2000.0 and 3000.0 μg/ml · kg. Details of the preparation and storage of ICI-50123 and the control solution have been presented previously[8]. 2 h after injection the rats were again anesthetized with ether and following esophageal ligation the stomach was removed. Gastric contents were carefully drained into centrifuge tubes, centrifuged for 10 min at 2500.0 g and then filtered through glass wool. Details of the methods of gastric juice analysis have been presented previously[9]. pH was determined using a Beckman Model 76 Expandomatic pH meter with a microelectrode attachment in a thermomatic constant temperature block. All results are expressed as mean values ± S.E.M.; p values were calculated using Student's t-test.

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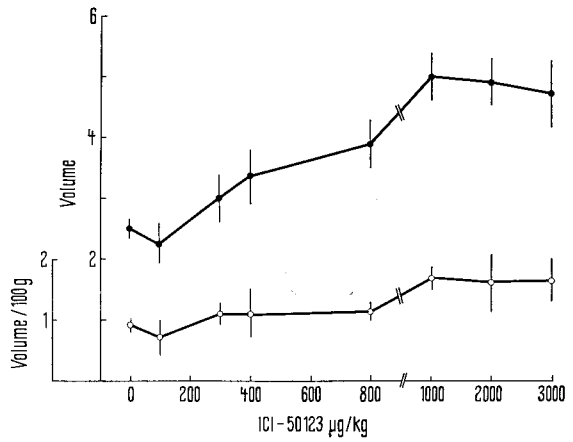

Fig. 1. Gastric juice volume in ml/2 h, (●) and volume/100 g in ml/100 g · 2 h, (○) in 2 h pylorus-ligated male rats as a function of ICI-50123 dose. Data are expressed as mean values ± S.E.M. from 10–20 rats/group.

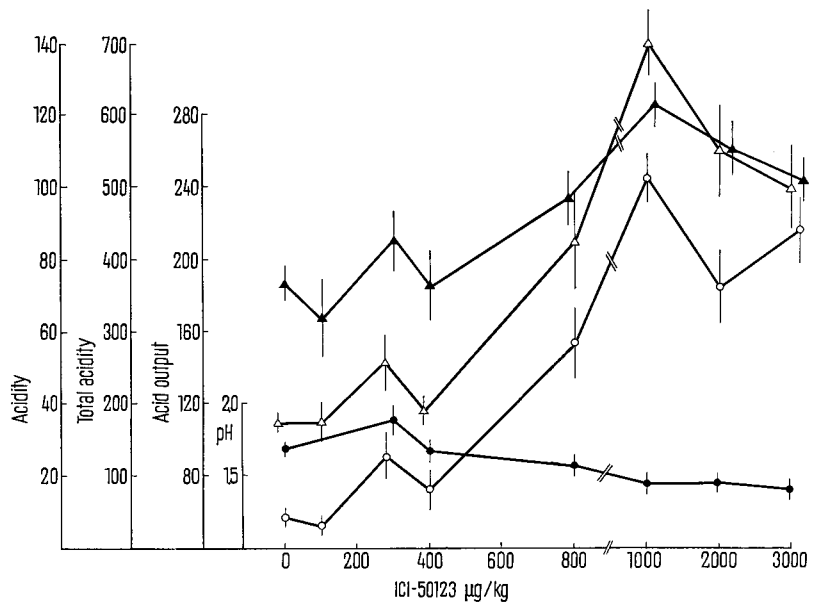

Fig. 2. Gastric juice acidity in mEq/l · 2 h. (△), total acidity in μEq/2 h. (▲), acid output in μEq/100 g/2 h. (○) and pH in units (●) in 2 h pylorus-ligated male rats as a function of ICI-50123 dose. Data are expressed as mean values ± S.E.M. from 10–20 rats/group.

Gastric juice volume and gastric juice volume/100 g[10,11] are indicated in Figure 1. Peak responses were obtained with 1000.0 µg/kg doses of ICI-50123 and are significantly different from injected control rats ($p < 0.001$). Increasing the dose 3-fold did not increase the response. Acidity, total acidity and acid output are indicated in Figure 2. Peak responses were obtained for these 3 parameters with doses of 1000.0 µg/kg and are significantly different from injected control rats ($p < 0.001$). Increasing the dose 3-fold depressed slightly acid production. Gastric juice pH (Figure 2) in control rats was 1.67 U. This fell to pH 1.35 at a dose of 1000.0 µg/kg ICI-50123 ($p < 0.05$). Increasing the dose 3-fold did not statistically increase the response.

The data presented in this report indicate that ICI-50123 is a powerful stimulant of Shay rat gastric secretion producing maximal volume and acid outputs with a dose of 1000.0 µg/kg s.c. This dose is far greater than that required to produce maximal stimulation in man[1], dog[3] and cat[2], and is roughly parallel to the response to histamine[9]. Maximal gastric juice volume, volume/100 g and acid output induced by ICI-50123 (Figures 1 and 2) are approximately similar to data obtained in Shay rats under maximal stimulation with histamine and insulin-induced hypoglycemia[9,12].

Large doses of hog gastrin given i.v. have been shown to depress acid gastric secretion[13]. As can be seen from this report supramaximal doses of ICI-50123 although not influencing gastric juice volume (Figure 1), minimally depress acidity, total acidity and acid output (Figure 2); p values are not significant[14].

Zusammenfassung. An männlichen Ratten wurden nach 2 h Pylorusligatur Magensaftmenge, Volumen/100 g Körpergewicht, pH, Azidität, gesamte Azidität und Säureproduktion bestimmt und als Funktion von ICI-50123 studiert. Eine maximale Stimulation erfolgte bei einer Dosierung von 1000.0 g/kg s.c. Eine Abnahme der Säureproduktion zeigte sich bei supramaximaler Dosis.

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Body Weight and Organ Sizes in Warmth-Adapted and in Cold-Adapted, Hibernating Golden Hamsters

When investigating hibernation under laboratory conditions, one should realize that the animals studied are not only prepared for and changed by the lethargy, but that they are also adapted to cold and to the prevailing light-dark rhythm as well as being subjected to seasonal fluctuations. The influence of the light-dark rhythm and of the season can be eliminated by the introduction of strictly paired observations on hibernating and control individuals. A subtraction of the results obtained in both animals of a pair will yield information pertaining directly to cold adaptation-hibernation, presuming that season and light-dark rhythm influence the hibernating hamster and its control in the same way.

Here, the observations will be reported, done on body weight and organ sizes in golden hamsters which were kept on hibernation in a long-term experiment. These data were compared with those obtained in adequate controls.

Material and methods. The material and the procedure have already been published previously (SMIT-VIS and AKKERMAN-BELLAART[1]). Measurements of the following organ weights were performed: testes, kidneys, adrenals, spleen, pancreas (after fixation in Bouin for 24 h), liver, heart (opened, rinsed and blotted), lungs, interscapular brown adipose tissue, skin and femora. The femora were included because they constitute a part of the body bearing no relation to thermoregulatory processes. The results of the weighings are listed in Table I. In order to study the adrenal cortex and medulla separately, their proportions in the total adrenal weight have been approximated by determining histometrically their respective volumes, assuming that the 2 tissues do not differ in specific gravity. The volume measurements of the 2 adrenals have been treated separately, because they had been fixed in different fixatives: left gland in Susa and right gland in Orth's, and, therefore, a different shrinkage may take place. The average quotient weight/volume amounted to 2.06 for the left and 2.45 for the right adrenal, demonstrating a higher degree of shrinkage in the Orth fixative. The results of the volume measurements are given in Table I.

With regard to the evaluation of the data, it is of importance that ROBINSON and WILBER[2] found a close correlation between the body weight on the one hand and the weights of some organs on the other. Based on this observation the assumption may be made that if there had been differences between the weights of the various organs of one hamster pair at the start of the experiment (both having the same body weight then!), these differences can be considered to be samples of a distribution with a mean value of zero. If, at the end of the experiment, such a distribution of differences in

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