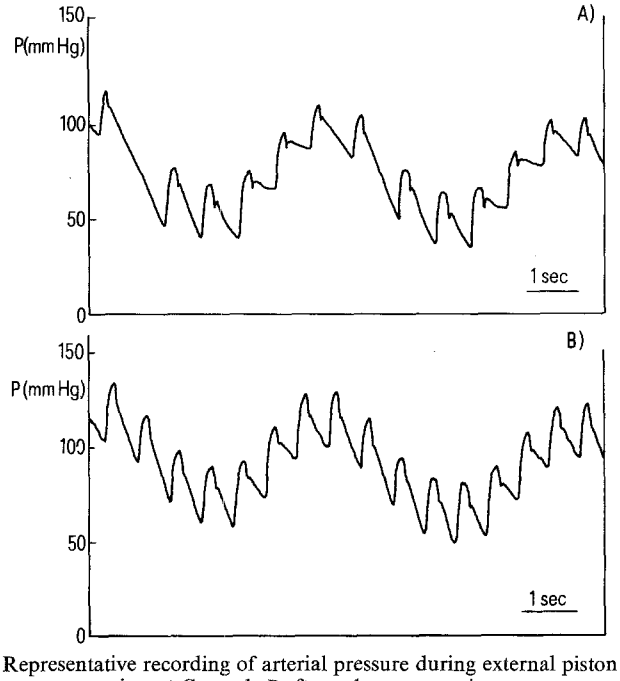
was inserted via the right femoral artery and positioned in the descending aorta at mid-heart level with the aid of a fluoroscope. Aortic pressure was digitized at a rate of 200 samples per sec and displayed on a digital oscilloscope (Nicolet Explorer III). Numerical values of time and pressure were available for each sample point. This oscilloscope was also capable of storing the data of each experimental run on magnetic disc for later analysis.

To test the sensitivity of the baroreflex, mean arterial blood pressure was fluctuated slowly around its mean. For this purpose, a sinusoidal piston pump was attached to the abdominal aorta by means of a cannula inserted into the left femoral artery. In operation, the cycle period was 5 sec and the stroke volume was adjusted to cause a 50 mmHg swing in mean arterial pressure. The increase in blood pressure caused a decrease in heart rate while the decrease in blood pressure caused an increase in heart rate (figure A). Because of the delay in the baroreflex the highest cardiac pulse interval (CPI) occurred after the peak in the arterial pressure. CPI's were measured during the pump cycle and normalized by dividing them by the CPI of the steady state prior to the pumping. As a measure of the baroreflex sensitivity the variability of all normalized CPI's for 1 pumping cycle was determined by calculating their SD.



Representative recording of arterial pressure during external piston pump operation. *A* Control; *B* after volume expansion.

In all animals, the effect of volume loading on the baroreflex sensitivity was evaluated by expanding the animal's blood volume by 30% with dextran 70 (Macrodex, Pharmacia Lab). The SD of the normalized CPI's obtained during pumping was again determined.

Results. The figure illustrates a representative experiment. Figure A depicts the effects of pumping on arterial pressure and heart rate under control conditions, while figure B shows the same variables after volume loading. The variability of the CPI's is significantly decreased after volume loading indicating a lower sensitivity of the baroreflex.

Volume expansion caused an average increase in central venous pressure of 4.0 ± 1.1 mm Hg and an average rise in mean arterial pressure of 19.2 ± 6.9 mm Hg. The heart rate increased by 6.8 ± 3.2 beats/min. The table presents the values of the SD of the normalized CPI's before and after volume expansion. The variability of the CPI's was lower after volume expansion in every experiment. Using a paired t-test it was shown that the decrease in this variability was significant at the 0.02 level.

Conclusion. The consistent and statistically significant decrease in the variability of the normalized CPI's after volume loading indicates that volume loading decreased the sensitivity of the heart rate response to blood pressure changes. It does not indicate the site of the reflex arch at which the changes occur. The results support the hypothesis proposed by Vatner et al.[2] and Stinnett et al.[4] that volume loading decreased the baroreflex sensitivity. However, in their experiments artifacts due to nerve stimulation or methoxamine effects could not be excluded. The purely mechanical stimulus used in the experiments presented here excludes these possible artifacts.

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The effect of caerulein on epithelial growth in the mouse gall bladder[1]

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Summary. Caerulein, a synthetic decapeptide, was injected into mice in order to study its effect on DNA-synthesis activity in the gall bladder epithelium. Histoautoradiography after the injection of labeled thymidine was used. Higher labeling indices were observed at 8, 12 and 24 h after caerulein injection. These data indicate that caerulein, apart from its cholecystokinetic effects, exerts a trophic effect on the gall bladder mucosa.

Several gastrointestinal polypeptide hormones have been shown to influence epithelial cell replication in the gastrointestinal mucosa or in the pancreas. Cholecystokinin (CCK-PZ) is known to promote DNA synthesis and growth in the pancreas[3], and to stimulate the secretion of glycoproteins in mouse gall bladder epithelium[4]. The decapeptide caerulein, which shows a striking resemblance to the C-terminal octapeptide of porcine CCK-PZ, has properties similar to CCK-PZ on the pancreas[5]. In the present study, caerulein was administered to mice in order to study its effect on DNA synthesis in the gall bladder mucosa, using a histoautoradiographic method.

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Mean gallbladder weight ± SEM in normal and caerulein-treated mice. According to the Willcoxon-test, the difference is not significant (NS)

	8 h	16 h	24 h
Normal	5.2 ± 0.6 mg	7.7 ± 1.4 mg	7.2 ± 1.5 mg
	NS	NS	NS
Caerulein	6.6 ± 0.7 mg	8.6 ± 1.0 mg	7.0 ± 0.8 mg

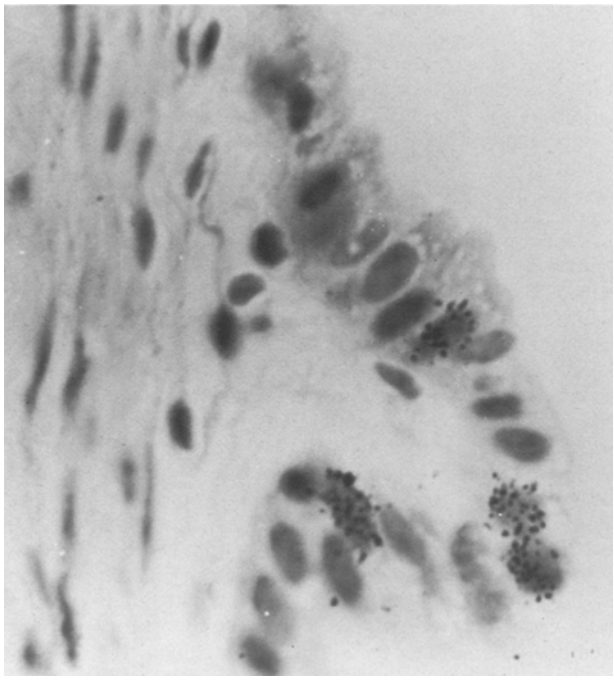

Fig. 1. Autoradiography of mouse gall bladder epithelium 1 h after the injection of tritiated thymidine. Labeled epithelial cells are seen.

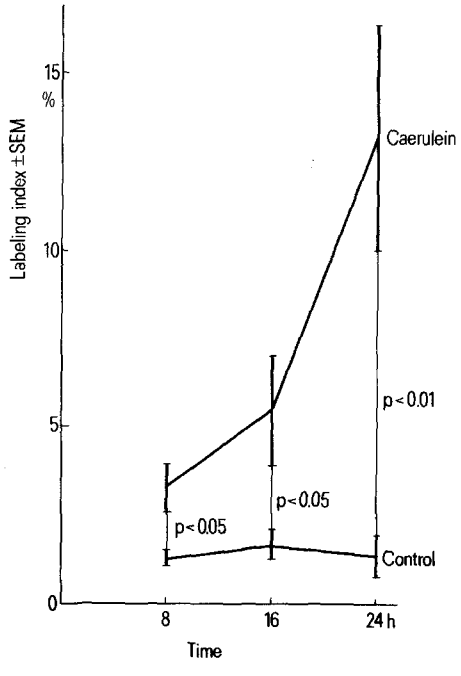

Fig. 2. Mean labeling indices (± SEM) in the gall bladder epithelium of mice at intervals after injection of 2 µg/kg/h caerulein and after the injection of saline (control).

Material and methods. 60 C57 B1/6 mice weighing 21.5–23.5 g were subdivided at random into 2 equal groups. The animals in group 1 were given 8 s.c. injections of 1 µg/kg of synthetic caerulein (Farmitalia, Milano) in 0.25 ml of saline at 30 min intervals between 12.00 h and 16.00 h. The animals in group 2 received simultaneous injections of saline only.

10 mice of each group were taken at random and were killed by neck dislocation at 8, 16 and 24 h respectively after the last injection. 1 h before killing, all animals were given an i.p. injection of 1 µCi/g b.wt of tritiated thymidine (Radiochemical Center, Mol, Belgium: sp. act. 5 Ci/mmole). Cholecystectomy was performed after ligation of the cystic duct near the gall bladder with 000 silk, and each ligated gall bladder, with its contents, was weighed. Thereafter, the gall bladder was opened. After 24 h fixation in 10% neutral formalin at 4 °C, the gall bladders were embedded in paraffin, and transverse sections, 3–4 µ thick, were taken from the midportion of the organ. Sections were covered with nuclear emulsion (Ilford K5 in gel form), developed after a 3-week exposure at 4 °C (Kodak Dektol developer) and stained with haematoxylin-eosin. In each gall bladder specimen the percentage of labeled cells (labeling index) was counted for a total of 2000 consecutive epithelial cells (figure 1).

Results. No difference in b.wt or in the weight of the ligated gall bladder (table) was observed between the 2 groups. After caerulein injection, an increase in the labeling index values of the gall bladder mucosa was observed. This effect was significant ($p < 0.05$) at 8 and 16 h, and became highly significant ($p < 0.01$) at 24 h (figure 2).

Discussion. Cholecystokinin has at least 2 target organs: the gall bladder, which it contracts, and the pancreas, where it has a secretory and a growth effect. Caerulein, an analogue of CCK-PZ, which has been synthetized, has similar biological effects.

Our data show that caerulein is able to induce proliferative changes in the gall bladder epithelium. A significant increase in DNA synthesis was observed 8 h after the administration of the polypeptide and the effect became even more significant later. The lag period between the injection of caerulein and the DNA-synthesis response was similar to that described in the gastrointestinal mucosa after injection of gastrin or pentagastrin[6,7].

The trophic effect of caerulein may be explained by a direct effect of the polypeptide on the gall bladder epithelium or by an indirect effect, for instance the mechanical stimulation induced by gall bladder contraction. At the time of killing, the gall bladders were not empty (table), but the duration of the cholecystokinetic effect of caerulein is less than the shortest interval (8 h) used in the present investigation[5] and the gall bladders might therefore have been refilled. Further studies in vitro are needed to investigate this point.

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