Progress report: Caerulein

Caerulein (I) is a decapeptide present in the skin of Hyla caerulea and other Australian hylid frogs, of Leptodactylus pentadactylus labyrinthicus and related South American leptodactylid frogs, and finally of the South African amphibian Xenopus laevis. The South American hylid frogs of the Phyllomedusa genus contain a decapeptide, phyllocaerulein (II), strictly related to caerulein. The amino acid sequences reported below clearly show the striking resemblance in chemical structure existing between the caeruleins, the C-terminal octapeptide of porcine cholecystokinin-pancreozymin (III) and the C-terminal hexapeptide of the gastrins II (IV).

(I) Pyr–Gln–Asp–Tyr(SO3H)–Thr–Gly–Trp–Met–Asp–Phe–NH2
(II) Pyr–Glu–Tyr(SO3H)–Thr–Gly–Trp–Met–Asp–Phe–NH2
(III) –Asp–Tyr(SO3H)–Met–Gly–Trp–Met–Asp–Phe–NH2
(IV) –Tyr(SO3H)–Gly–Trp–Met–Asp–Phe–NH2

Extensive pharmacological investigations have demonstrated that the chemical similarity is accompanied by a close resemblance in the pharmacological effects displayed by the caeruleins and the gastro-duodenal hormones. However, whereas the spectrum of activity of caerulein presents only a partial overlapping with that of gastrin, it is very similar or identical to that of cholecystokinin-pancreozymin.

Gastrin is a potent stimulant of gastric secretion, a moderate stimulant of pancreatic secretion, and a poor stimulant of the motility of the gallbladder and small intestine. On the other hand, both caerulein and cholecystokinin-pancreozymin are formidable stimulants of the musculature of the gallbladder and the intestine, powerful stimulants of pancreatic secretion, and relatively moderate stimulants of gastric secretion.

On account of the common C-terminal pentapeptide, antibodies to human gastrin I were capable also of binding caerulein molecules. However, these were much less effective than human gastrin I in competing for binding sites on antibodies to human gastrin I. The degree of binding of caerulein was of the same order as gastrin antibody binding of cholecystokinin-pancreozymin and pentagastrin.

This article reports the present status of research on caerulein, considering the main target organs of the polypeptide separately.

Gallbladder and Bile Ducts

The gallbladder in situ or as an isolated preparation was highly sensitive to caerulein. A few nanograms per kilogram of weight injected intravenously were sufficient to stimulate the organ in situ and less than 1 ng/kg/min was effective when infused intravenously. The isolated gallbladder was contracted by caerulein in concentrations as low as 0.03–2 ng per ml of nutrient solution. There was no tachyphylaxis but, generally, a good dose response relationship. The spasmogenic action of the polypeptide was atropine resistant.
In anaesthetized animals the threshold intravenous dose capable of causing contraction of the gallbladder in situ was 0·3-1·5 ng/kg for the guinea-pig, 0·125-0·25 ng/kg for the cat, and 5-10 ng/kg for the chicken.\(^6,7,8\)

These doses were similar to those which were found to be effective by the radiographic technique on the human biliary tract and on that of the unanaesthetized dog.

In the dog the threshold cholecystokinetiс doses by intravenous and subcutaneous routes were 1 and 10 ng/kg, respectively. The gallbladder contraction began very soon and lasted three to four hours after intravenous administration and six to seven hours after subcutaneous injection. In some instances a certain degree of contraction was appreciable up to 24 hours. The cholecystokinetiс activity was more striking after subcutaneous than after intravenous administration, except for threshold doses. Also the intrahepatic and extrahepatic bile ducts were apparently contracted by caerulein. On a molar basis caerulein was 16 times as potent as cholecystokinin-pancreozymin and 170 times as potent as both gastrin I and gastrin II.\(^9,10\)

In a dog suffering from ‘cystic mucinous hypertrophy’, caerulein was able to remove the gelatinous inspissated mucus from the gallbladder, with subsequent ejection of the material into the duodenum.\(^11\)

No untoward reactions were observed, except after intravenous doses larger than 1 µg/kg, which caused retching and evacuation of formed stools or diarrhoea.

So far, caerulein has been employed, for cholecystographic studies, in more than 200 patients. Doses were 5-30 ng/kg by the intravenous route, 0·25-1 µg/kg by intramuscular injection, and 0·75-1 µg/kg by nasal insufflation. The threshold intravenous dose was of the order of 1 ng/kg. The spasmogenic action of the polypeptide began soon after the injection, reached its peak after 10 to 15 min, and disappeared after 90 min; 2·5 to 5 ng/kg of intravenous caerulein produced a response very similar to that caused by a fatty meal.

Caerulein elicited a contraction of the gallbladder even after failure of fatty or egg yolk meals and often provoked a good visualization of the cystic and the common bile ducts. Moreover, a premedication with caerulein apparently permitted a reduction in the amount of intravenous contrast medium required for cholangiography.

Extrapolating from the data in the literature it would appear that caerulein is at least three times more potent than cholecystokinin-pancreozymin, on a molar basis.

In contrast to the gallbladder musculature, the smooth muscle of the sphincter of Oddi(choledocho-duodenal junction) was relaxed by caerulein and this effect was particularly evident when the tone of the sphincter was elevated, either spontaneously or following premedication with spasmogenic drugs.\(^14\) As a consequence of the relaxation of the sphincter of Oddi the choledochal resistance was lowered and bile flow increased in conscious dogs. Of the peptides examined, the most potent relaxant was caerulein.\(^15\)

**Gastrointestinal Musculature**

In the intact, conscious dog, caerulein caused emesis and evacuation of the bowel. The mean effective dose by rapid intravenous injection was 0·4-0·5 µg/kg, and by subcutaneous administration 3-4 µg/kg. By intravenous infusion caerulein produced retching in most dogs when doses exceeded 10 ng/kg/min.

The musculature in situ of the gastrointestinal tract was highly sensitive to caerulein. Intravenous doses as low as 1-5 ng/kg had a spasmogenic
Caerulein

action on jejunal loops of the dog, and slightly larger doses contracted the small intestine of the cat. The stomach and the large intestine seemed to be somewhat less sensitive to the polypeptide. Caerulein also displayed a considerable spasmogenic action on the rat pylorus. All these effects, with the exception of the latter, could be reduced or abolished by atropine.6

One mole of caerulein produced the same stimulant action on a dog jejunal loop as the following number of moles of other compounds: cholecystokinin 6, human gastrin I 40-50, bradykinin 300, physalaemin 5, edeoisin 6, angio-ensin 30, carbachol 150, and vasopressin, acetylcholine, histamine, 5-hydroxytryptamine, eserine, prostigmine, and pilocarpine > 1,000.18

The intramuscular injection of 1 µg/kg of caerulein in a dog produced the evacuation of a big faecaloma resistant to the usual stimulants of intestinal motility.17

In the chicken, the polypeptide given by intravenous infusion increased frequency and amplitude of the movements of both the proventriculus and the duodenum. Threshold doses were of the order of 5 and 0.25 ng/kg/min, respectively. Atropine abolished the effect on the proventriculus, but not on the duodenum.8

In human subjects studied by a balloon method caerulein caused inhibition of the duodenal motility and stimulation of the jejunal motility and tone. Threshold doses by intravenous infusion were of the order of 1 ng/kg/min. The effect subsided five minutes after the infusion had been discontinued. By the subcutaneous route the threshold dose was 25-30 ng/kg. With 0.75 µg/kg the stimulant effect lasted 30 to 40 minutes.

In small bowel contrast studies it could be seen, by fluorography and cinematography, that caerulein administration (1-2 ng/kg/min by infusion or 0.5-1 µg/kg by intramuscular injection) produced a conspicuous reduction in the transit time of the contrast medium. The barium took only 20 to 30 min to reach the colon and peristalsis was very lively. Not infrequently the contrast medium was present simultaneously in the colon and the stomach.

In two children suffering from Hirschprung-like aganglia, caerulein, infused at a rate of 3 ng/kg/min, produced an intense stimulation of the colon, as evidenced by a balloon method. In three patients with paralytic ileum resistant to the usual therapy (enema, prostigmine), caerulein infused for two to five hours at a rate of 3 ng/kg/min produced emission of gas and faeces and then complete canalization of the intestinal tube.17

Isolated preparations of the gastrointestinal tract were in general fairly insensitive to caerulein and tachyphylaxis was frequently observed.6

Pancreas

EXOCRINE PANCREAS
Caerulein displayed a potent stimulant action on pancreatic secretion. In the anaesthetized dog with an acutely cannulated Wirsung duct threshold doses were 1-5 ng/kg by rapid intravenous injection, 0.25-1 ng/kg/min by intravenous infusion, and 50-100 ng/kg by subcutaneous injection. By infusion the response was proportional to the dose up to 100 times the threshold dose. There was a conspicuous increase not only in the volume of the flow of pancreatic juice but also in the output of solid constituents of the juice and of amylase. However, continuous stimulation of the pancreas by intravenous infusion of caerulein resulted in a progressive reduction in the amylase concentration and even more in the dry residue of pancreatic juice. The bicarbonate concentration was similar to that observed after the administration of cholecystokinin-pancreozymin.18

In conscious dogs provided with chronic pancreatic fistulas the dose of
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caerulein required for 50% of maximal response was 0.5 ng/kg/min, volume output, and 0.7 ng/kg/min, enzyme output. Depending on experimental conditions, caerulein was seven to 50 times more potent than gastrin, and three to six times more potent than cholecystokinin-pancreozymin on pancreatic juice flow and enzyme output. Secretin, however, stimulated flow 2.5 to 20 times more than caerulein, on a molar basis.

In the narcotized cat caerulein was completely devoid of any secretin activity but injected after priming injections of secretin was 2.5 times more effective than cholecystokinin-pancreozymin.

Repeated subcutaneous injections of caerulein increased up to 100% the amylase and the chymotrypsin content of the rat pancreatic tissue.

Concomitantly with, and probably resulting from, the stimulation of pancreatic secretion there was an increase in the blood flow through the duodenal-pancreatic artery. Intravenous doses of caerulein active on this vascular area (1-2 ng/kg) were at least 10 times lower than those causing systemic hypotension.

ENDOCRINE PANCREAS

In the dog given an intravenous infusion of caerulein (threshold 0.5-1 ng/kg/min) the radioimmunological technique revealed increased amounts of insulin in the venous blood returning from the pancreas. With the threshold dose of caerulein the increase of insulin was 100-250%, with 25 ng/kg/min it was up to tenfold. The effect lasted as long as the infusion was continued with a peak after 10 min, followed by a steady rate of secretion which was about 50% of the peak. Discontinuing the infusion caused a prompt return to basal values; recommencing the infusion resulted in a renewed release of insulin. After rapid intravenous injection (threshold 10 ng/kg) the peak was reached within one minute, and the effect lasted five to 20 min, depending on the dose. From preliminary experiments it appeared that caerulein caused release of glucagon too.

Brunner's Glands

The intravenous infusion of 2.5 ng/kg/min of caerulein stimulated the Brunner glands of the dog to produce 0.56 ml of secretion per 15 min, and the glands of the cat to produce 0.36 ml of secretion per 60 minutes. The rate of secretion was sustained at these levels throughout the infusion and fell to control levels within 30 min of discontinuing the infusion. In the dog the effect produced by the above dose of caerulein was greater than that caused by 7 ng/kg/min of secretin, 3 μg/kg/min of histamine, and 70 ng/kg/min of both porcine gastrin II and cholecystokinin-pancreozymin.

Liver

At high dose levels (0.05-0.2 μg and 1 μg/kg, respectively, by rapid intravenous injection) caerulein stimulated the flow of hepatic bile in the dog and the rat. The dry residue of the bile and the cholesterol concentration were appreciably greater in rats treated with caerulein than in control rats.

In sharp contrast to the above poor effectiveness, caerulein proved to be highly active on the chicken hepatocytes. Doses as low as 0.5-1 ng/kg/min given by intravenous infusion were capable of increasing the flow of hepatic
Caerulein

 bile and output of solid constituents of the bile. Moreover, at the same dose levels caerulein conspicuously increased the transport of sulphobromophthalein through the hepatocyte, as shown by the reduction of and levels forms.27 

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Stomach

In the denervated fundic pouch of the dog, caerulein increased the rate of flow of gastric juice and the output of acid and pepsin. Pepsin concentration in caerulein juice was up to three times greater than in control juice. Threshold doses were 4-8 ng/kg/min by intravenous infusion, and 0-25-0-5 μg/kg by subcutaneous administration. Rapid intravenous injection was ineffective.28

The dose of caerulein given by intravenous infusion needed to produce one half the calculated maximal response was 8 ng/kg/min for acid secretion and 6 ng/kg/min for pepsin secretion. In gastric fistula dogs the same dose was as low as 2-7 ng/kg/min, for acid secretion.7

On both a molar and a weight basis caerulein has been found to be more potent than gastrin in stimulating acid secretion. However, it should be pointed out that gastrin was capable of producing much higher observed and calculated maximal responses than was caerulein. Calculated and observed acid outputs to maximal doses of gastrin were usually twice those found for caerulein. Caerulein then was extremely potent in that low doses produced significant amounts of secretion, but it was not effective in producing high rates of acid secretion comparable to those seen with maximal doses of gastrin or histamine. However, caerulein stimulated as much pepsin secretion as gastrin and, on a molar basis, was three to seven times more potent than cholecystokinin-pancreozymin.7,20

Sustained acid secretion of the dog fundic pouch produced by gastrin infusion was reduced by caerulein infusion (3 ng/kg/min). However, the effect of caerulein on acid secretion elicited by histamine infusion varied according to the doses of both histamine and caerulein. Low doses of caerulein generally increased the secretion produced by intermediate doses of histamine; high doses of caerulein inhibited the secretion produced by high doses of histamine.

Atropine completely inhibited acid secretion produced by caerulein.28,29

When tested on the acid secretion of the perfused rat stomach preparation, the threshold dose of caerulein by rapid intravenous injection was 25 ng/kg, by intravenous infusion 4 ng/kg/min, and by subcutaneous injection 0-25-0-5 μg/kg. A clear dose-response relationship could be observed. The action of caerulein was resistant to atropine, but was sharply reduced by pretreatment of the animals with the histamine liberator 48/80 and potentiated by pretreatment with aminoguanidine. When caerulein was given by rapid intravenous injection during a priming infusion of histamine its effect was enhanced and considerably prolonged. In the rat, caerulein was seven to 45 times more potent than human gastrin I, on a molar basis, and three times more potent than cholecystokinin.28,30

Caerulein proved to be a potent stimulant of gastric secretion also in the chicken, especially when administered by intravenous infusion. The effect was abolished by atropine.31

Approximately 50 Trials were also carried out on human subjects. The threshold intramuscular dose of caerulein was 50-100 ng/kg and the optimum response was obtained with 250 ng/kg. At this dosage the effect lasted 60-90 min and peak gastric secretion (40 ml juice and 3-2 m-equiv total HCl
output) was reached between 15 and 30 minutes. During the course of the response to 250 ng/kg of caerulein, 35 m-equiv Cl⁻, 10 m-equiv Na⁺, and 5 m-equiv K⁺ were secreted.²²

However, besides acting as a stimulant, caerulein could act also in man as an inhibitor of gastric secretion. In fact, when a caerulein infusion (100 ng/kg/hr) was superimposed upon an infusion of pentagastrin (1µg/kg/hr), the gastric acid secretion produced by the gastrin-like peptide was reduced by 70%.²³

Systemic Blood Pressure

Caerulein affected blood pressure in all the animal species experimented upon. However, response varied considerably from one species to another, and doses required to elicit changes in blood pressure were considerably higher than those acting on secretions and motility of the gut.

In the dog caerulein elicited hypotension in nearly all conditions with no signs of tachyphylaxis. Threshold doses were 10-100 ng/kg by rapid intravenous injection, 5-15 ng/kg/min by intravenous infusion, and 5-10 µg/kg by subcutaneous injection. Caerulein was more potent than bradykinin, but considerably less potent than either physalaemins or edeoisins. Hypotension produced by caerulein had a slower onset but a much greater duration than that caused by the above peptides. On a molar basis, caerulein was at least 50-100 times more potent than human gastrin I and four to eight times more potent than cholecystokinin-pancreozymin. Atropine reduced caerulein hypotension, α-adrenergic blocking agents enhanced it.

The rabbit behaved like the dog in the response to caerulein. The cat, the rat, and the chicken were less sensitive and erratic responses were seen.

Intradermal injections of caerulein into the human forearm caused the appearance of a wealing reaction very similar to that produced by bradykinin. At threshold doses (20-50 ng) caerulein was approximately as active as bradykinin, at larger doses less active.²⁴

Structure Activity Relationship of Caerulein-like Peptides

So far, in addition to caerulein and phyllocaerulein, about 60 caerulein-like peptides have been synthesized at the Farmitalia Laboratories for Basic Research, Milan. Some definite conclusions can be drawn from their systematic screening on a number of test objects:²⁵,²⁶

1 Whereas the characteristic spectrum of activity of the gastrins seems to depend largely on the C-terminal pentapeptide, the spectrum of activity of caerulein and of cholecystokinin-pancreozymin depends on the C-terminal heptapeptide, a necessary prerequisite for activity being the presence of an O-sulphated tyrosyl residue at the N-terminus of the heptapeptide. Both desulphation of the tyrosyl residue and a shift of this residue, as in gastrins, towards the C-terminus produced a conspicuous reduction in biological activity. Desulphated caerulein was six to 20 times less active than caerulein on the gastric secretion of the dog, 20 times less active on the pancreatic secretion of the dog, and more than 100 times less active on the motility of the gallbladder and intestine.²⁷

2 Substituting the sulphuric acid with a phosphoric acid residue, substituting the para-tyrosyl residue with a meta-tyrosyl residue, bromination of the tyrosyl residue all produced a drastic reduction in activity. On the contrary, considerable activity was retained after chlorination of the tyrosyl
Caerulein

residue or after substitution of a D-tyrosyl for the L-tyrosyl residue.

3 The activity of the caerulein heptapeptide was fully retained or even slightly increased by substitution of the threonyl residue by a methionyl residue (C-terminal heptapeptide of cholecystokinin-pancreozymin), a norleucyl residue, or an a-aminobutyryl residue. Substitution of the methionyl residue by a norleucyl residue caused a definite increase in activity.

4 By adequate changes in the caerulein molecule it has been possible to dissociate, to some extent, the action of the polypeptide on smooth muscle from that on secretory cell, the action on gastric secretion from that on pancreatic secretion, and even the action on exocrine pancreas from that on endocrine pancreas. Trends of present research are mainly in this direction.

Obviously, most of the above conclusions also apply to cholecystokinin-pancreozymin.

On a molar basis, the C-terminal heptapeptide of caerulein retained 20 to 60% of the total spectrum of activity of caerulein, while the C-terminal heptapeptide of cholecystokinin possessed 50 to 80% of the activity of caerulein, being more potent than cholecystokinin itself.

These observations raise the question of whether cholecystokinin-pancreozymin is the true hormone released by the duodenal mucosa after the passage of the chyme from the stomach to the intestine. Cholecystokinin-pancreozymin with its 33 amino acid residues and a molecular weight of 3900 might simply be a carrier polypeptide from which a smaller hepta- or octapeptide, with a molecular weight of 1028 or 1143, is split off and liberated into the circulation when the flow of bile and pancreatic juice as well as intestinal movements are necessary for digestive processes.

Moreover, the high potency of caerulein on the endocrine pancreas on the one hand and on the hepatic cell on the other, would support the hypothesis that the gastroduodenal hormones in general, and cholecystokinin-pancreozymin in particular, have a more complex and global function than so far suspected. In fact, in addition to stimulating the exocrine function of the pancreas and motility of the gallbladder and the gut, cholecystokinin, as inferred partly from caerulein studies, might inhibit gastrin-evoked gastric secretion, might prepare the pancreas for the secretion, or even cause the secretion of insulin and glucagon, and finally might stimulate, in some direct or indirect way, the activity of the hepatocytes.

The mechanism of action of caerulein may be different in different animal species and on different smooth muscles or secretory cells. Where atropine produced a clear-cut inhibition a cholinergic mechanism may be postulated, eg, gastric secretion of the dog and the chicken, gastrointestinal motility of the dog; where the effect was atropine-resistant a direct action on the effector cell is conceivable, eg, gallbladder contraction, pancreatic secretion, or an action mediated through other active substances (perhaps histamine for the gastric secretion of the rat).

Studies in progress are designed to investigate the action of caerulein on intestinal secretion and excretion as well as on intestinal absorption in the hope of obtaining a complete panorama of the actions of this highly active and versatile polypeptide, and hence of cholecystokinin-pancreozymin.

The only cholecystokinin so far isolated and investigated is porcine cholecystokinin. However, it is highly probable that, as for the gastrins, there are several species-specific cholecystokinins capable of displaying different hormonal activities, at least quantitatively. In this case it would be interesting to assess how much of the activity can be attributed to the C-terminal heptapeptide and how much to the remaining amino acid chain.

Experimental results obtained in man and laboratory animals unequivocally demonstrated that intravenous infusion was the best way of administering caerulein, followed by subcutaneous or intramuscular injection. This is not surprising, since by these routes caerulein is made available to the target
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organisms for a longer period of time. It should be stressed that gastrointestinal hormones are released physiologically into the bloodstream by prolonged infusion and not by abrupt discharge.

In the clinical trial, a simple and practical method for administering caerulein, like pentagastrin, could be nasal insufflation. The efficiency of nasal absorption was confirmed also in the anaesthetized dog with cannulation of the trachea and consequent exclusion of the pulmonary system.37

Untoward side effects in man after the administration of caerulein were rare and could be seen only at high dose levels, eg, > 10 ng/kg by rapid intravenous injection, > 5 ng/kg/min by intravenous infusion, and > 1 μg/kg by the subcutaneous or intramuscular route. They consisted of a sensation of heat in the face with sweating, abdominal discomfort with borborygmi, nausea, and vomiting. All these symptoms disappeared spontaneously within a few minutes of intravenous injection or of discontinuing an intravenous infusion.

In summing up, it may be concluded that caerulein and some caerulein-like hepta- and octapeptides are extremely effective compounds, showing an extraordinary selectivity of action on the musculature and secretory glands of the digestive tract. These peptides have all the prerequisites necessary for them to be considered excellent substitutes for cholecystokinin-pancreozymin in all the clinical and experimental uses of the duodenal hormone.

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