A New CCK-B/Gastrin Receptor Antagonist Acts as an Agonist on the Rat Pancreas

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Summary

The new CCK-B/gastrin receptor antagonist PD 136450 is of potential value in treating neurologic and psychiatric disorders. We investigated possible side effects on the rat pancreas using acute and chronic administration schedules. In chronic experiments, four groups of rats were given either PD 136450, the proton pump inhibitor BY 308 (in order to induce hypergastrinemia), a combination of both, or control solutions over 14 d. Pancreatic growth, DNA, and protein content were significantly increased in rats given PD 136450 irrespective of circulating gastrin levels. Furthermore, an anticoordinate shift in pancreatic enzyme content in favor of trypsin and chymotrypsin at the expense of amylase and lipase was observed. Plasma CCK levels remained unchanged in this group making a role of circulating hormone unlikely. In order to investigate a possible direct agonistic effect of the CCK-B/gastrin receptor antagonist, we studied amylase release from isolated rat pancreatic acini in response to PD 136450 and sulfated CCK8 alone and in combination with the specific CCK-A receptor antagonist MK 329. Increasing concentrations of PD 136450 caused a monophasic dose–response curve in contrast to the well-known biphasic amylase release in response to CCK8. Addition of increasing doses of PD 136450 to a concentration of CCK causing maximal stimulation of amylase release (0.1 nM) further enhanced amylase release from pancreatic acini. The specific CCK-A receptor antagonist MK 329 dose-dependently inhibited CCK8- and PD 136450-induced amylase release. In conclusion, the new CCK-B/gastrin receptor antagonist PD 136450 exhibited profound agonistic actions on the rat pancreas mediated via CCK-A receptors.

Key Words: CCK-B/gastrin receptor; CCK-B/gastrin receptor antagonist; CCK-A receptor; pancreatic enzyme secretion; pancreatic growth; cholecystokinin, gastrin.

Introduction

Cholecystokinin and gastrin are structurally and functionally related peptides acting through specific receptors. These receptors have been classified as CCK-A and CCK-B receptors on the basis of peptide affinity and binding of receptor antagonists. CCK-A receptors are widely distributed throughout the gastrointestinal tract, and are highly selective for sulfated CCK analogs and the nonpeptide receptor antagonist MK 329 (formerly L-364,718) (1,2). Only a few brain areas contain CCK-A receptors (3). The vast majority of cerebral CCK receptors belongs to the CCK-B type with only marginally higher affinity for sulfated CCK analogs over nonsulfated peptides.
of the CCK/gastrin family, but high affinity to the receptor antagonist L-365,260 (3–5).

Because of diverging binding affinities of agonists, and antagonists the existence of a third type of receptor, the gastrin receptor, has been proposed (6). Gastrin and sulfated CCK bind with equal affinity to this receptor located on the parietal cell (6). The canine parietal cell gastrin receptor has recently been sequenced (7). In rats, the structure of the pancreatic and cerebral CCK-A receptor and the cerebral CCK-B receptor has been described (8,9). In addition, there is now evidence that CCK-B and gastrin receptors are identical in rats and man (10).

In the brain, CCK₈ is thought to act as neurotransmitter, and seems to play a role in neurologic and psychiatric disorders (11). Highly specific CCK receptor antagonists offer a new tool in the therapy of these diseases. Furthermore, CCK/gastrin receptor antagonists are particularly useful in determining the role of CCK and gastrin under physiological and pathophysiological conditions.

Recently, a new class of centrally and peripherally acting CCK-B/gastrin receptor antagonists has been developed (12–14). The α-methyltryptophan derivative PD 136450 (compound no. 27 in ref. 13) has proven a potent inhibitor of gastrin/CCK-mediated actions in the brain and gastrin-mediated effects in the periphery (13,15). Binding studies using mouse cerebral cortex and rat pancreas revealed a severalfold higher specificity and potency compared to the benzodiazepine derivative L-365,260 (13), which has so far been known as the most powerful CCK-B/gastrin receptor antagonist. However, before new CCK/gastrin receptor antagonists can be used as therapeutic agents, their precise effect on CCK/gastrin-mediated actions must be defined in the central nervous system and the periphery.

In the course of a study investigating the effect of the newly developed CCK-B/gastrin receptor antagonist PD 136450 on gastric endocrine cells subjected to chronic achlorhydria (16), we determined its action on the exocrine pancreas. In addition, the direct acute effect of the antagonist was studied using isolated pancreatic acini. We thereby could show that the CCK-B/gastrin receptor antagonist exhibited profound agonistic actions on the exocrine pancreas of the rat. Stimulation characteristics suggest this antagonist/agonist to be of potential value in further characterizing high- and low-affinity binding sites of the CCK-A receptor in the pancreas.

**Methods**

**Chronic Experiments**

**Study A**

Female Sprague-Dawley rats weighing 220–240 g were used throughout the study. They were housed in cages in groups of four at a light/dark cycle of 12 h each. The animals had free access to water and regular lab chow. Four groups of eight rats each were formed and treated for 14 d with the following substances:

1. PD 136450 plus vehicle for BY 308, a proton pump inhibitor;
2. BY 308 plus vehicle for PD 136450;
3. BY 308 plus PD 136450;
4. Vehicles only (controls).

The CCK-B/gastrin-receptor antagonist PD 136450 (former name: CAM 1189; Parke Davies, Cambridge, UK; compound no. 27 in ref. 13) was dissolved in saline and injected sc every 8 h (54 μg/kg body wt/d). In acute experiments, this dose had been shown to antagonize pentagastrin-stimulated gastric acid secretion completely for at least 8 h (15). No loss of effect was observed during a 2-wk period of administration (15). The proton pump inhibitor BY 308 (5-trifluormethyl-2-(4-methoxy-methyl-2-pyridyl-methyl)-thio<1H>benzimidazol; Byk Gulden, Konstanz, Germany) was used at a dose of 40 μg/kg body wt/d to induce achlorhydria and hypergastrinemia (17). The substance was dissolved in methocel and administered once per day in the morning via an orogastric tube. The last drug dose was administered 2–4 h prior to exsanguination of 12-h fasted animals. During the 2-wk treatment period, blood was drawn from the retroorbital vein plexus for gastrin measurements in all groups before and 1, 4, 7, and 14 d after starting of drug administration.

**Study B**

In a second set of experiments, rats were treated according to the protocol described above. In contrast to study A, animals had access to lab chow until they were sacrificed.