**Introduction**

More than 40 peptides are known to exist in mammalian neurons, where they serve chemical-messenger functions [1, 2]. In most instances, however, we lack the pharmacological tools, in the form of non-peptide-drug molecules, which act as agonists or antagonists at neuropeptide receptors. The example of morphine shows, however, that a single, non-peptide structure can provide all the information needed to develop large numbers of synthetic compounds with agonist or antagonist actions [3]. More recently, synthetic opiates have been developed with selectivity for the \( \mu \), \( \delta \) and \( \kappa \)-receptor subtypes [4]. It seems likely that the 1990s will see rapid advances in the development of non-peptide drugs acting at peptide receptors. Important advances have been made recently in the discovery of lead compounds acting at the receptors for angiotensin II [5] and substance P [6]. This paper will review the discovery and development of novel synthetic drugs acting at cholecystokinin (CCK) receptors.

**Discovery and development of synthetic CCK antagonists**

The Merck compounds all derive from a natural-product lead, asperlicin (Fig. 1), from the fungus *Aspergillus alliaceus* [7]. This was discovered in a screening programme using the binding of radioiodinated CCK-8S to CCK receptors in rat pancreatic membranes as the primary assay. Asperlicin proved to have submicromolar potency in displacing \(^{125}\text{I}-\text{CCK-8S} \) and acted as a competitive antagonist of the contractions elicited by CCK-8S in guinea pig ileum and gall bladder with similar submicromolar potency [7].

Using asperlicin as a lead for medicinal chemistry, it proved possible to simplify this complex, heterocyclic molecule and to synthesize more potent derivatives. Devazepide (also known as L-364718 and MK-329) was one such synthetic derivative (Fig. 1), approximately 100-fold more potent than the natural product [8]. Like asperlicin, devazepide has selectivity for the CCK-A receptors found in gastrointestinal-tract tissues, and has considerably lower affinity for the CCK-B receptors in brain, or gastrin receptors in stomach (Table 1). Further medicinal chemistry research, however, led to the discovery of compounds with the reverse selectivity, e.g. L-365260 (Fig. 1, Table 1) [9, 10]. L-365260 exhibits high affinity for both gastrin receptors and CCK-B sites in brain. Indeed all of the synthetic compounds in the Merck series exhibit similar affinities for the gastrin- and CCK-B receptors, suggesting that these are possibly identical.

**Functional studies in vivo**

Devazepide inhibited CCK-stimulated gall-bladder contraction, pancreatic exocrine secretion and colonic contraction [11]. In pilot studies in human volunteers orally administered devazepide (10 mg) effectively prevented the CCK-induced increase in plasma pancreatic-polypeptide (PP) levels. Devazepide also blocked post-prandial increases in PP, while having no effect on plasma insulin-, glucagon- or glucose-responses to a mixed meal [12]. Thus, devazepide offers a valuable research tool for studying the physiological role of CCK in regulating pancreatic endocrine function in man.

The CCK-B/gastrin antagonist, L-365260, has a number of effects in vivo. As predicted, the compound acts as an inhibitor of gastrin-induced gastric-acid secretion [10], although there is little effect on basal levels of acid secretion. In terms of central nervous system effects, attention has focused on three topics: (i) Analgesia. There is evidence that CCK acts as a functional antagonist of opiates [13], and CCK antagonists have been found to have the opposite effect, i.e. to enhance opiate-induced analgesia. In addition, the CCK antagonists were able to inhibit the development of tolerance to the analgesic effects of morphine on chronic treatment [14, 15]. (ii) Feeding. CCK is thought to play an important role as a ‘satiety factor’. CCK antagonists, as predicted, can increase food intake in otherwise satiated animals, and devazepide (but not L-365260) is able to block the satiety effects of exogenously administered CCK [16, 17]. (iii) Panic/anxiety. Intravenously administered CCK-4 or pentagastrin are remarkably effective in eliciting brief panic attacks in human subjects [18, 19].
animals exogenously administered CCK-4 also appears anxiogenic in reducing exploratory behaviour of animals placed in a novel or fear-provoking environment [20, 21]. L-365 260 is able to block the anxiogenic effects of CCK-4 or pentagastrin. L-365 260 is also active in animal models thought to be predictive of anxiolytic drugs; these include the elevated-plus-maze, punished-drinking and light-dark-box paradigms [21, 22].

L-365 260 is not the only CCK-B antagonist in development. Recently, a chemically unrelated compound PD134308 was described, derived by rational design from the C-terminal sequence of CCK. This compound also demonstrates high affinity and selectivity for CCK-B sites in brain. Studies in vivo have shown that, like L-365 260, it also enhances opiate analgesia, blocks the anxiogenic effects of pentagastrin, and displays anxiolytic activity in animal behavioural models [21, 23, 24]. In addition, a series of quinazolines with nanomolar affinity and high selectivity for CCK-B sites has been described, derived by rational design from asperlicin [25].

**Clinical applications**

It is too early to predict whether the novel synthetic CCK antagonists will have important therapeutic applications. CCK-A-selective compounds such as devazepide might have utility in treating pancreatic disorders and in the control of excessive gut motility. Devazepide itself, however, caused an abnormal incidence of gall stones in long-term animal-toxicity studies, suggesting that chronic use of such compounds may not be possible.

With CCK-B/gastrin-selective compounds there are a number of potential applications; to control gastric-acid secretion, to enhance appetite and food intake in conditions of anorexia, to enhance the effectiveness of opiate analgesics and to inhibit the development of tolerance to such drugs, and in the
Inhibitory-concentration values giving 50% inhibition ($IC_{50}$ values) are presented for devazepide and L-365 260 as dis-
placers of the specific binding of $^{125}$I-gastrin in gastric glands, and $^{125}$I-CCK-8S in brain and pancreas of guinea pig. These
reflect binding to gastrin, CCK-A and CCK-B receptors, respectively. Values are means ± SEM for at least three determin-
tations; data from [10].

<table>
<thead>
<tr>
<th>Test compound</th>
<th>$^{125}$I-Gastrin</th>
<th>Brain</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>0.9 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>Gastrin</td>
<td>3.0 ± 1.0</td>
<td>4.0 ± 1.0</td>
<td>560.0 ± 230.0</td>
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<tr>
<td>Devazepide</td>
<td>300.0 ± 7.20</td>
<td>250.0 ± 97.0</td>
<td>0.08 ± 0.03</td>
</tr>
<tr>
<td>L-365 260</td>
<td>1.1 ± 0.4</td>
<td>2.0 ± 0.3</td>
<td>280.0 ± 33.0</td>
</tr>
</tbody>
</table>

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