Symmetry in drug molecules

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The use of haemoglobin as a model drug receptor (Beddell, Goodford, Norrington, Wilkinson & Wootton, 1976) has led to the hypotheses that some drug or hormone molecules may show symmetrical features because they interact with symmetrical receptors (Beddell, Sheppey, Blundell, Susaki, Dockerill & Goodford, 1977), and that receptors may be divided into two distinct classes: symmetric and assymetric (Goodford, 1978). To explore this proposal further it is desirable to have a method of measuring the symmetry of a drug molecule.

The concept of symmetrical receptors arises by analogy with known proteins composed of subunits arranged symmetrically about a diad axis. Hence one is concerned with diad symmetry, and it is possible to calculate the 'best' diad axis of a drug molecule if its conformation is known, and if some of the atoms can be paired with each other. The 'best' axis gives the lowest root mean square deviation between each atom of a pair and the 180° rotated position of its partner. For a perfectly symmetrical molecule this is zero, and every atom has a partner unless it lies in the symmetry axis. However perfect symmetry does not often occur, although symmetrical features can sometimes be detected. Thus for 11 selected atom pairs in trimethyl-(+)-tubocurarine, in the crystal conformation observed by Sobell, Sakore, Tavale, Canepa, Pauling & Petcher (1972), the root mean square deviation is 0.11 nm.

The plausibility of the 'best' axis may be assessed by comparing atomic positions before and after 180° rotation. Moreover this test can be applied to all the atoms in the molecule, and is not restricted to the original subset which were used to define the 'best' axis. One would expect chemically similar groups to exchange places with each other after rotation if the symmetrical features of the compound were related to the symmetry of its receptor, and the pseudosymmetry of trimethyl-(+)-tubocurarine passes this test.

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Blockade of 5-hydroxytryptamine (5-HT) receptors by quipazine

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During the assessment of the agonist activity of various substances at ganglionic 5-HT receptors, quipazine (2-(1-piperazinyl) quinoline maleate) was tested. Quipazine has been reported to behave as an agonist in various smooth muscle preparations (Hong & Pardo, 1966) and in the CNS (Rodriguez, Rojas-Ramirez & Drucker-Colin, 1973; Green, Youdim & Grahame-Smith, 1976), probably acting at 5-HT receptors. In the rabbit isolated superior cervical ganglion, quipazine had negligible agonist activity, but proved to be an antagonist of 5-HT.

Gangia were mounted in a sucrose-gap apparatus and change in resting membrane potential recorded at room temperature. Small volumes of a solution containing 5-HT or a nicotinic agonist were injected into the superfusion stream and the resulting depolarizations displayed on a chart recorder. When the ganglion was superfused with quipazine in a concentration of 5 μM or greater, responses to 5-HT were completely blocked (3 experiments); at a concentration of 1 μM block was complete in 3 of 6 experiments and greater than 75% in the others; a concentration of 0.1 μM produced about 75% blockade (5 experiments). The blockade was slow in onset and, although not readily reversible, was highly selective since responses to nicotinic agonists, such as trimethylammonium and dimethylphenylpiperazinium (DMPP), were not depressed. Quipazine (1 μM) usually caused a substantial enhancement of responses to DMPP.

Some actions of 5-HT in the CNS may also be antagonized by quipazine. In the spinal cord, the dorsal root potential (DRP) evoked by stimulating an adjacent dorsal root is thought to reflect depolarization of the primary afferents. DRPs were recorded from the isolated cord of the neonate rat maintained at 21°C. Eight successive responses were averaged electronically and displayed on a chart recorder. 5-HT (1 and 100 μM) depressed DRP amplitude by 27 ± 5% (n = 14) and 45 ± 6% (n = 14), respectively (mean ±s.e. mean). After superfusing with quipazine (0.01 μM) for

at least 10 min, 5-HT (1 and 100 μM) depressed DRP amplitude by 6 ± 2% (n = 15) and 3 ± 1% (n = 7), respectively. No depression by 5-HT was observed in the presence of quipazine (1 μM) in 4 experiments.

In preliminary experiments, quipazine has been shown to antagonize contractions of rat fundus induced by 5-HT. Stomach strips were superfused at 37°C with Krebs solution. The dose-response curve to 5-HT was displaced to the right in a non-parallel manner, suggesting a non-competitive mode of antagonism. PT_{50} values were obtained by determining the negative log of the molar concentration of quipazine which reduced the maximal effect of 5-HT by 50%. This value is around 6.9.

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The mechanism of 5-hydroxytryptamine-induced pressor responses in ganglion-blocked anaesthetized dogs

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The cardiovascular actions of 5-hydroxytryptamine (5-HT) *in vivo* are complex. However, in ganglion-blocked anaesthetized dogs 5-HT produces dose-dependent vasopressor responses which are thought to result from stimulation of excitatory receptors for 5-HT in vascular smooth muscle (Stone, Wenger, Ludden, Stavorski & Ross, 1960; Saxena, Houwelingen & Bonta, 1971). We have carried out experiments to determine the nature of the receptors involved.

Male and female beagle dogs (7–10 kg) were anaesthetized with thiopentone (25 mg/kg i.v.) and barbitone sodium (300 mg/kg i.p.). Blood pressure and heart rate were recorded and drugs were administered via the right femoral vein. Ganglion-blockade was produced by mecamylamine (5 mg/kg i.v.).

5-HT (1–30 μg/kg i.v.) produced dose-related increases in arterial pressure and heart rate. The vasopressor action of 5-HT, but not of phenylephrine, was antagonised in a dose-dependent manner by the 5-HT antagonists methysergide (10–100 μg/kg i.v., Figure 1) and cyproheptadine (10–100 μg/kg i.v.). However, the 5-HT-induced vasopressor action was also antagonised by phentolamine (0.3–3.0 mg/kg i.v., Figure 1), reduced by bilateral adrenalectomy and abolished by syrosingopine pretreatment (0.5 mg/kg i.v. 48 h and 1.0 mg/kg i.v. 24 h previously).

We conclude that most, if not all, of the 5-HT-induced pressor response in ganglion-blocked anaesthetized dogs results from catecholamine release, of which a major component arises from the adrenal glands. This release process appears to be susceptible to blockade by methysergide and cyproheptadine and could therefore involve a D-receptor-mediated depolarization by 5-HT of the chromaffin cells in the adrenal medulla (see Douglas, Kanno & Sampson, 1967).

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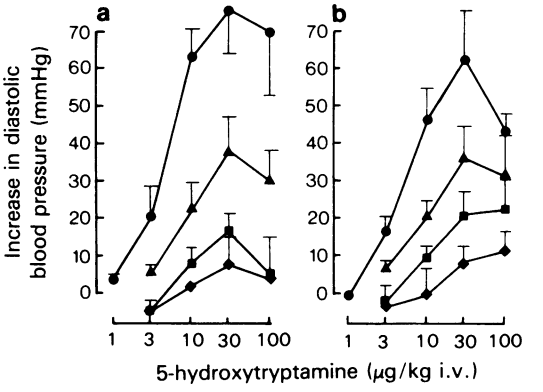

Figure 1 Mecamylamine-treated anaesthetized dog. Antagonism of the vasopressor effects of 5-HT by (a) methysergide (▲10, ■30 and ◆100 ug/kg i.v.) and (b) phentolamine (▲0.3, ■1.0 and ◆3.0 mg/kg i.v.). Control observations in the absence of antagonist (●). Each point is the mean value (± s.e. mean, n = 4).