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