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As Good as Chocolate

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No one could have imagined how important the 1948 discovery of the vasoconstrictor serotonin (5-hydroxytryptamine or 5-HT) would be to the field of human physiology (1). Elucidation of the 5-HT structure (2) and synthesis of the molecule with the expected biological activity (3) soon followed. This monoamine is a ligand for 15 receptors, and drugs that target 5-HT receptors are widely used to treat conditions including migraine headache, depression, anxiety, nausea, vomiting, and irritable bowel syndrome, reflecting the wide diversity of physiological and pathophysiological processes in which 5-HT is involved (4). On page 615 and 610 in this issue, Wacker *et al.* (5) and Wang *et al.* (6), respectively, report the crystal structure of human 5-HT_{2B} bound to the antimigraine agent ergotamine and compare it with the 5-HT_{1B}-ergotamine structure. Together with biochemical and computational data, these structures reveal molecular mechanisms responsible for divergent signaling patterns of ergotamine, serotonin, and the psychedelic drug lysergic acid diethylamide (LSD).

The structures were obtained by fusing either receptor to a thermally stabilized bacterial protein [apocytochrome b562RIL (BRIL)]. This approach stabilizes the receptor to promote crystallization but does not alter ligand-binding properties. The structural information, together with computational ligand-docking experiments, reveal similar binding modes for ergotamine, 5-HT, and LSD to the ligand-binding pocket formed by residues conserved in the 5-HT receptor family, thereby clarifying the family-wide agonist activity of 5-HT. However, there are some key differences between the two receptors (see the figure). In both structures, an accessory binding pocket adjacent to the binding site for the natural ligand (5-HT) can accommodate chemical groups located distal to the core indoleamine moiety in a differential manner, which possibly could control signaling. The 5-HT_{1B} receptor displays a 3 Å outward shift at the extracellular end of helix V relative to the 5-HT_{2B} receptor, resulting in a more open, extended pocket that explains receptor subtype selectivity for ligands.

5-HT receptor subtypes are classified according to their ligand-binding preferences, sequence homology, and signaling mechanisms. With the exception of the type 3 receptor, which is a ligand-gated cation channel, all 5-HT receptors are seven-transmembrane receptors belonging to the rhodopsin-like class A group that transmit signals to heterotrimeric GTP-binding proteins (G proteins) and other effectors like β -arrestins (7). Many 5-HT receptors display a close evolutionary relationship with receptors for other

biogenic amines (such as the neurotransmitters dopamine and norepinephrine). This, along with structural similarities among the biogenic amines themselves, explains why drugs that target specific 5-HT receptors are especially prone to produce untoward side effects through “off target” receptors. One example is the severe vasoconstriction that can result from supratherapeutic doses of ergot alkaloids, which are thought to exert their beneficial antimigraine effects through 5-HT_{1B}, and 5-HT_{1D} receptors but also can act on α -adrenergic receptors with dangerous consequences (8). Another prominent example is the fibrotic cardiac valvulopathy (thickening of heart valves) associated with a metabolite of fenfluramine that can act on the 5-HT_{2B} receptor. Fenfluramine is a component of the notorious and now defunct anorexogenic drug combination Fen-Phen (9), whose recall was the largest in U.S. history (10).

Rational drug design, in which the known structure of an endogenous agonist of interest is used as a basis to generate derivatives with potential selectivity for a subset of receptors, has played an important role in developing more selective 5-HT receptor–targeting drugs with improved side-effect profiles (11). A prime example is the 5-HT₁–selective “triptans,” which are the drug class of choice for treating migraine headache. The 5-HT receptor structures will guide the tailoring of candidate drug molecules to bind selectively to particular receptor subtypes. Differences in the ligand-binding pockets of the 5-HT_{1B} and 5-HT_{2B} receptors could, for example, be exploited to eliminate agonist effects at the 5-HT_{2B} site that are associated with cardiotoxicity.

At first glance, structures of these receptors appear highly similar to that of rhodopsin, the first G protein–coupled receptor (GPCR) whose structure was solved by x-ray crystallography (12). Indeed, pairwise root mean square deviations (RMSDs) between the 5-HT receptors and rhodopsin are ~2.3 to 2.7 Å among the core of ~260 C α positions (or ~80% of the receptor sequence), demonstrating a structural triumph whereby the same overall GPCR topology is maintained despite markedly different amino acid sequences (13). However, the differential ligand- and effector-binding specificity of the structures provides an important pharmacological story. Wacker *et al.* and Wang *et al.* could determine the 5-HT_{1B} and 5-HT_{2B} receptors, respectively, in the presence of the same ligand. By comparing the two structures, they noted differences in the intracellular region that interacts with G proteins or arrestins. Both receptors show biased signaling, in which agonists preferentially activate one pathway over the other. The comparison revealed that ergotamine biases the signaling of 5-HT_{2B} through β -arrestin by inducing conformational changes within the cytoplasmic portion of the receptor that are distinct from changes observed in the 5-HT_{1B} structure that enable coupling to G proteins. Such structural insights can open a whole new avenue of investigation of ligand-induced differential signaling.

The serotonin receptor family is like the mythical Roman god Janus, often depicted with two faces pointed in opposite directions. These receptors can be dangerous, like 5-HT_{2B}, which is often referred to as a death receptor because of its cardiotoxic effects. On the other hand, chocolate, which contains high concentrations of the serotonin precursor tryptophan and serotonin-like monoamines, elicits cravings through these same receptors and brings much pleasure to our lives (14). Structural information about GPCRs continues to have important implications for developing new pharmaceuticals (15). We can look forward to the design of

noncardiotoxic 5-HT receptor ligands that will make the outcome of stimulating these receptors as good as chocolate.

Acknowledgments

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Uncovering bias in serotonin receptor signaling

(A) Natural (serotonin/5-HT) and synthetic (ergotamine and LSD) serotonin receptor ligands have a common indole amine structure (blue) at their core. (B) Crystallographic structures of the human 5-HT_{1B} (left) and 5-HT_{2B} (right) receptors in a complex with ergotamine (orange). The BRIL fusion protein used to facilitate crystallization is shown as a white surface. (C) Ergotamine stabilizes distinct conformations in the two 5-HT receptors, providing a structural explanation for the biochemically observed phenomenon of biased signaling.