Serotonin (5-HT) receptors are involved in numerous central nervous system functions. Several different serotonin receptor subtypes are known to exist. The 5-HT_2_ subgroup of receptors plays an important role in appetite control, anxiety, depression, and so forth. However, the 5-HT_2_ receptor subtypes display high homology and present a significant challenge for the development of ligands specific to a precise receptor subtype. Now, Shashack et al. (DOI: 10.1021/cn200077q) present an approach for the development of specific ligand antagonists for the 5-HT_2AR receptor.

Some 5-HT receptors exist as dimers and even oligomers. A possible approach for targeting these multimeric receptors is through the use of multivalent compounds. Using this rationale and a Ca^{2+} release bioassay, the authors developed a dimeric form of the known 5-HT antagonist, M-100907. This dimeric derivative displays high specificity and affinity to 5-HT_2AR and achieves its highest potency when two molecules of M-100907 are attached via a linker of 12–18 atoms in length. Pairing multimeric ligands to pair with multimeric receptors to increase specificity is an approach which may have broad application in drug development.

**DISC1: FROM GENE TO PROTEIN TO THERAPEUTIC OPPORTUNITY**

About a decade ago, *Disrupted in schizophrenia 1* (*DISC1*) gene was first identified in a family with high propensity to mental illness. Since the initial discovery, a large volume of published data implicates *DISC1* as a genetic risk factor for a variety of psychiatric disorders including schizophrenia, bipolar disorder, and major depression. In this issue, Soares et al. (DOI: 10.1021/cn200062k) scrutinize and discuss the emergent literature on the DISC1 protein. The authors meticulously evaluate and integrate structural and bioinformatic predictions on DISC1 with the experimental biochemical and genetic data. They carefully filter and tabulate interacting regions of all known DISC1 binding partner proteins and provide a systematic analysis of known disease-associated sequence variants. Within the review, the authors highlight and discuss unresolved issues in the field and describe in detail the therapeutic pathways to which DISC1 has been linked, that show the most “druggable” potential, with an emphasis on its known interactions with 3',5'-cyclic phosphodiesterase-4 (PDE4, the target for mood stabilizer rolipram) and glycogen synthase kinase-3β (GSK3β, the target for lithium, a commonly used drug to treat bipolar disorder).

**NEW ROUTE FOR CNS THERAPEUTIC DELIVERY**

Intravenous (i.v.) injection is a common mode for administering central nervous system (CNS) therapeutics. In conjunction with the increased delivery efficiency of nanoparticle carriers, i.v. injection increases bioavailability of administered pharmacological agents. However, use of i.v. injection also significantly increases the risk of spreading disease via contaminated syringes. In the current issue, Yuan et al. (DOI: 10.1021/cn200078m) search for safer administration routes with compatible new nanoparticle therapeutic carriers. The authors examined the buccal membrane in the oral cavity for an alternative drug administration site for systemic circulation. To develop drugs that can cross the membrane, highly branched dendrimers were used as suitable carriers for transbuccal drug delivery. An opioid peptide and CNS drug, DPDPE, was conjugated to a polyamidoamine dendrimer along with polyethylene glycol (PEG), which increases tissue absorption. These dendrimers were fluorescently labeled and administered to porcine buccal mucosa for mechanistic and permeability studies. These experiments demonstrated the utility of the buccal mucosa for delivery of nanoparticle CNS drugs and may provide a safe alternative to i.v. injection for drug delivery.

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