Positive-allosteric modulation of the 5-HT_{2C} receptor: implications for neuropsychopharmacology and neurotherapeutics

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Serotonin (5-hydroxytryptamine; 5-HT) was identified in the mammalian brain in the 1950s. We now recognize brain 5-HT to actualize flexible and complex actions directed by binding to at least 14 5-HT receptors as well as the serotonin reuptake transporter. The 5-HT_{2C} receptor (5-HT_{2C}R) is a G protein-coupled receptor (GPCR) that has been implicated in psychiatric and neurological disorders, including anxiety, depression, schizophrenia, and substance use disorders as well as obesity. The orthosteric 5-HT_{2C}R site, at which the endogenous agonist binds, has been a primary target for ligand discovery for obesity based upon the role of 5-HT_{2C}R in the control of feeding, energy and glucose homeostasis, yielding the first-in-class 5-HT_{2C}R agonist lorcaserin (Belviq®) approved by the FDA for weight loss. While 5-HT_{2C}R antagonism potentially mediates the side effect of some antipsychotics (e.g., clozapine) to increase weight gain, the development of 5-HT_{2C}R antagonists has been pursued for the treatment of anxiety disorders and depression. Importantly, selective agonists and antagonists have advanced knowledge of 5-HT_{2C}R neuropsychopharmacology.

Binding of 5-HT to the 5-HT_{2C}R results in a conformational change that catalyzes the diffusion of multiple second messenger effectors and G protein-dependent signaling. An allosteric modulator is a ligand that binds to a spatially distinct allosteric site(s) and alters the receptor conformation to modulate its interaction with other ligands and/or signal transduction molecules [1]. Higher sequence divergence for allosteric sites is expected across receptor subtypes relative to the highly conserved orthosteric domain. Such allosteric modulation is saturable (comes to a finite magnitude when the allosteric site is fully occupied) and probe-dependent (varies dependent upon the orthosteric ligand) with the prospects for separate control of affinity and efficacy. A positive- (PAM) or negative-allosteric modulator (NAM) can enhance or inhibit the functional response to an orthosteric agonist, while silent allosteric ligands are suggested to compete with PAMs or NAMs at the allosteric binding site. Additionally, allosteric ligands can be antagonists or agonists with, or without, PAM or NAM activity (e.g., ago-PAMs, ligands that potentiate agonists and display intrinsic efficacy).

Small molecule 5-HT_{2C}R PAMs would not act as an orthosteric agonists (as does lorcaserin), but instead act at distinct allosteric site(s) on the 5-HT_{2C}R and potentiate signaling of an orthosteric ligand (Fig. 1). The first identified 5-HT_{2C}R PAM was the fatty acid oleamide [2], which lacked selectivity against other GPCRs. In 2003, chemical library screening resulted in the discovery of an analogue of the antibiotic lincomycin, PNU-69176E, as a selective 5-HT_{2C}R PAM [3]. In 2012, Zhou and colleagues optimized the synthetic route to generate PNU-69176E and its diastereomer [4],

Fig. 1 The orthosteric and allosteric sites on the 5-HT_{2C} receptor are distinct. Serotonin binds to the orthosteric site to generate downstream signaling. The 5-HT_{2C}R PAM CYD-1-79 (*cis*-4-alkylpiperidine-2-carboxamide series) increases 5-HT efficacy through actions at the allosteric site [5]

and we have recently designed, synthesized and characterized a series of new chemical entities as selective 5-HT_{2C}R PAMs [5]. Several molecules potentiated 5-HT_{2C}R-evoked signaling in vitro without displaying 5-HT_{2C}R efficacy or altering 5-HT_{2A}R signaling. CYD-1-79 exhibited a favorable overall pharmacokinetic profile, potentiated 5-HT_{2C}R-mediated behaviors, and attenuated impulsive action and sensitivity to cocaine-associated cues in a preclinical self-administration model. This series of 5-HT_{2C}R PAMs is complemented by the discovery of a 5-HT_{2C}R PAM, which suppressed food intake in rodents [6]. Thus, the chemical space for discovery of novel 5-HT_{2C}R neuroprobes and therapeutics is now expanding to include allosteric 5-HT_{2C}R modulators, providing the opportunity to explore cellular mechanisms of action, functional selectivity, neurochemical mechanisms, and neural sites of action for 5-HT_{2C}R to control behavior.

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Motion mapping in humans as a biomarker for psychiatric disorders

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Measuring movement has been a cornerstone of studying behavior in animals in controlled studies.

Movement data have served as a primary window into behavior, and by proxy, social function, mood, and cognition [1]. In humans, variations in locomotor activity have served as markers of a range of psychiatric syndromes including major depression, bipolar disorder, anxiety, catatonia, and substance use disorders [2]. Reports of sensor-based motion measurement in humans date back to the 1950s [2], and motion-based models of human psychopathology have been key to developing animal models of psychopathology [1]. A vast literature has documented how these animal models have facilitated development of motion-based signatures of antidepressant, anxiolytic, and other drug effects and guided drug development [3]. However, the limitations of technology thus far have meant that motion-mapping in humans has remained largely restricted to experimental settings.

Phenotyping of naturalistic human behavior continues to depend on self-report or observer-report measures, with sampling often at intervals of hours to days. Newer technologies, supported by advances in wireless connectivity, more compact and reliable sensors and devices, and higher computing power can now sample movement at intervals of seconds, and can facilitate measurement of human motion in the natural living environment in ways previously not possible [4]. Such technologies are setting the stage for movement to become a major new phenotypic biomarker in neuropsychiatry.

A wide array of validated technologies can quantify motion. These range from active sensors that move along with the body (e.g., accelerometers, gyroscopes), passive “line of sight” technologies (e.g., cameras, thermal sensors, and lasers), passive technologies that can detect motion through walls (e.g., radio wave sensors) and positioning technologies (e.g., GPS, satellite imaging) [5]. It is now possible to track individual contractions of facial muscles (used in computer vision and analysis of micro emotions), complex motions such as smoking or drinking coffee

[6] or even the movement of an individual across a global geographic field. Work in this new emerging field necessitates collaborative teams with a range of expertise that includes hardware development, signal processing, big data processing and analytics, machine learning, data visualization, and clinical implementation.

Early work in this field has demonstrated feasibility of translating this intensive sensor-based approach to clinical research. As an example, our group has demonstrated that by measuring how low frequency radio signals bounce off the human body and objects in a defined space (up to 800 sq.ft.), it is possible to elicit gait speed, gait patterns and spatial location. Using clinical correlation, we have established that these data can serve as markers of apathy, pacing, and disrupted circadian rhythms in patients with dementia [5].

A marker of the maturing of this field is recent NIH investment into major collaborative initiatives such as the MD2K initiative [7], which supports the acceleration of translating motion sensor data into validated biomarkers of behavior. While the need for privacy and security around sensor data is well recognized, innovative solutions around secure data storage and transfer will be crucial to this approach gaining widespread acceptance and use [4].

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