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Commentary

The Serotonin 5-HT_{2C} Receptor in Medial Prefrontal Cortex Exerts Rheostatic Control over the Motivational Salience of Cocaine-Associated Cues: New Observations from Preclinical Animal Research

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Drug addiction is a progressive, chronic brain disorder that ravages the health and lives of people globally. In the last century, pioneering discoveries in addiction science have begun to put to rest misconceptions concerning the nature of addiction and to yield new breakthroughs, which are poised to revolutionize its prevention and treatment. Importantly, addiction is now recognized as a disordered integration of cognitive and motivational aspects of reward-directed behavior involving higher order limbic-corticostriatal structures (Kalivas and Volkow, 2005). The medial prefrontal cortex (mPFC) and associated circuits are particularly sensitive to plasticity incurred due to repeated pairing of environmental stimuli (eg, drug paraphernalia, *etc*) with exposure to abused drugs. These associations between environmental cues and drug-taking are essential drug-associated memories that can trigger conditioned emotional responses in addicts and 'craving' (desire for drug), oft cited to explain relapse to drug-seeking and drug-taking during abstinence.

The cortical control of drug-seeking is the focus of a new study by Janet Neisewander and her colleagues reported in *Neuropsychopharmacology* (Pentkowski *et al*, 2010). These studies concentrate on cocaine dependence; cocaine abuse spirals to addiction in upwards of 15% of cocaine users and limited therapeutic options to suppress recidivism are available. Pentkowski *et al* (2010) have uncovered a nuanced neural circuit that selectively restrains the frontocortical circuitry that controls drug-seeking behavior in rats. In the procedure employed here, intravenous catheters were surgically implanted and rats were trained to lever press to deliver an intravenous injection of cocaine plus several associated environmental cues (ie, light and tone, sound of infusion pump). Following training of the cocaine self-administration, rats were subjected to extinction during which lever presses did not result in administration of cocaine or the associated cues. Subsequent to extinction, rats were given an injection of cocaine or were presented with the cue stimuli, previously associated with cocaine delivery, either of which then 'reinstated' cocaine-seeking. This cocaine-seeking in rats parallels the experience of an abstinent cocaine addict exposed to either a dose of cocaine or the environment in which cocaine use occurred. These exposures often result in relapse, which cycles into a loss of behavioral control and habitual drug use. This self-administration/reinstatement model employed in preclinical studies of cocaine abuse and addiction provides a valid method to explore the neural mechanisms and circuitry underlying cocaine-seeking and cocaine-taking.

Pentkowski *et al* (2010) have extended our understanding of how neurotransmission through the 5-HT_{2C} receptor (5-HT_{2C}R) within the mPFC controls drug-seeking. The 5-HT_{2C}R is characterized to regulate cognition, feeding, satiety and mood, although 5-HT_{2C}R dysregulation is thought to contribute to the neuromolecular mechanisms underlying the etiology of a variety of neuropsychiatric disorders including addiction, depression and schizophrenia. The 5-HT_{2C}R is localized to the postsynaptic specialization of neuronal synapses in mPFC neurons (Anastasio *et al*, 2010) and controls the excitability of mPFC neurons to afford a dynamic influence over a variety of cortically mediated autonomic, motor and limbic functions. In the Pentkowski *et al* (2010) study, microgram quantities of a drug were infused into one of three mPFC different subregions to activate the 5-HT_{2C}R signalosome before analysis of cocaine- or cue-evoked reinstatement. Pentkowski *et al* (2010) found that local stimulation of the 5-HT_{2C}R in the prelimbic and infralimbic subregions of the mPFC did not alter cocaine-taking, but did

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dose-dependently suppress reinstatement of cocaine-seeking behavior, an effect reversed by co-infusion of a selective 5-HT$_{2C}$R antagonist. Microinfusions of the 5-HT$_{2C}$R agonist into the anterior cingulate cortex were without effect in either paradigm. Thus, Pentkowski *et al* (2010) reveal that the control afforded by the mPFC 5-HT$_{2C}$R is specific to cocaine-seeking over cocaine-taking, and localized to more ventral mPFC subregions.

These results are interpreted as reflecting 5-HT$_{2C}$R-evoked decrements in the incentive-motivational value of the cocaine-primed and cue-elicited cocaine-seeking behavior. The mechanisms underlying suppression of cocaine-seeking by intra-mPFC infusion of a 5-HT$_{2C}$R agonist are likely to occur through stimulation of the 5-HT$_{2C}$R located on gamma-aminobutyric acid (GABA) interneurons or glutamate projection neurons that regulate mPFC output (Bubar and Cunningham, 2008) possibly via actions at the level of dopamine neurotransmission from the ventral tegmental area to limbic corticostriatal circuits known to be involved in goal-directed behaviors (Kalivas and Volkow, 2005). Future research is required to test this hypothesis; however, given the postulated role for hypofrontality and cognitive deficits in compulsive addictive disorders (Kalivas and Volkow, 2005), these new preclinical data from Pentkowski *et al* (2010) are important in identifying the 5-HT$_{2C}$R as a functional rheostat for mPFC output within the circuit that links motivational aspects of cues associated with drug reward with the cognitive control over drug-seeking behavior. It is possible that the connection between the cocaine experience and the need to seek this drug after repeated self-administration has been carved into the mPFC in part via 5-HT$_{2C}$R-mediated neuroplasticity developed during repeated pairings of this appetitive reward and its associated conditioned stimuli.

The mPFC is integral to the storage and maintenance of long-term memories, and the knowledge that these processes are malleably regulated by serotonergic neurotransmission through the 5-HT$_{2C}$R, encourages the design of preclinical experiments to decipher the role of the mPFC 5-HT$_{2C}$R in the acquisition, consolidation, retrieval and reconsolidation of cocaine-associated memories (Nic Dhonnchadha and Cunningham, 2008). Pre- and post-training administration of specific 5-HT$_{2C}$R ligands into discrete mPFC subregions would allow analysis of whether this receptor is involved in the acquisition of the pairing between cocaine and associated cues, or can disrupt the consolidation or retrieval of the memory of the cocaine–cue association in the self-administration paradigm, respectively. Furthermore, evidence that consolidated memories become labile again after 'reactivation,' that is, soon after the memory is retrieved by reminder stimuli that apparently reactivate the original memory trace, as is the case in the cue-reinstatement model, may provide an additional window in which to manipulate long-lasting cocaine-associated memories. Thus, manipulation of 5-HT$_{2C}$R signaling in the mPFC at various intervals following a retrieval session would further delineate the role of this system in reconsolidation of cocaine-associated memories. Preclinical evaluations of the role of 5-HT$_{2C}$R in acquisition, consolidation, retrieval and associated memory processes (eg, reconsolidation) and their special properties *vis à vis* drug-associated cues will help to identify how 5-HT$_{2C}$R-selective pharmacotherapic strategies may be useful to selectively minimize the strong incentive-motivational pull of cocaine-associated cues potentially imprinted as memory within mPFC circuits.

The observations reported by Pentkowski *et al* (2010) support the assertion that selective activation of the 5-HT$_{2C}$R signalosome may prove therapeutically useful to reduce craving and extend abstinence (Bubar and Cunningham, 2008). However, the progress of selective 5-HT$_{2C}$R agonists from preclinical evidence of efficacy to verification of safety and efficacy as psychotherapeutic medications in humans has been stymied until recently. Phase II and III clinical trials evaluating the efficacy of the selective 5-HT$_{2C}$R agonist lorcaserin (formerly APD 356, Arena Pharmaceuticals) for weight reduction have been successfully completed (Smith *et al*, 2009). Lorcaserin, which exhibits $\sim$15-fold and $\sim$100-fold greater potency to stimulate the 5-HT$_{2C}$R over the homologous 5-HT$_{2A}$R and 5-HT$_{2B}$R, respectively, was well tolerated by subjects in the weight reduction trials (Smith *et al*, 2009). Further, when evaluated in polydrug users, the doses shown to be therapeutic in obesity (Smith *et al*, 2009) were well tolerated, exhibited low abuse liability, and were not associated with notable neurocognitive or perceptual effects (Schram *et al*, 2009). The selective 5-HT$_{2C}$R agonist vabicaserin (SCA-136; Wyeth Research/Pfizer) has been under evaluation to establish its efficacy and safety in subjects with an acute exacerbation of schizophrenia. Vabicaserin exhibits an interesting profile as a selective 5-HT$_{2C}$R full agonist, a 5-HT$_{2B}$R antagonist and a very weak 5-HT$_{2A}$R antagonist (Sharon Rosenzweig-Lipson, personal communication). Thus, armed with the knowledge from present Pentkowski *et al* (2010) study, further preclinical studies to elucidate the functional regulation of meso- and allo-cortical circuitry by the 5-HT$_{2C}$R involved in the learning and memory processes relevant to cocaine self-administration and reinstatement, and the potential availability of two potent and selective 5-HT$_{2C}$R agonists opens the door to implementation of clinical research to evaluate these compounds as innovative pro-abstinence, anti-relapse therapeutics for stimulant addiction.

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REFERENCES

Anastasio NC, Lanfranco MF, Bubar MJ, Seitz PK, Stutz SJ, McGinnis AG *et al* (2010). Serotonin 5-HT$_{2C}$ receptor protein expression is enriched in synaptosomal and post-synaptic compartments of rat cortex. *J Neurochem* **113**: 1504–1515.

Bubar MJ, Cunningham KA (2008). Prospects for serotonin 5-HT$_2$R pharmacotherapy in psychostimulant abuse. *Prog Brain Res* **172**: 319–346.

Kalivas PW, Volkow ND (2005). The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* **162**: 1403–1413.

Nic Dhonnchadha BA, Cunningham KA (2008). Serotonergic mechanisms in addiction-related memories. *Behav Brain Res* **195**: 39–53.

Pentkowski NS, Duke FD, Weber SM, Pockros LA, Teer AP, Hamilton EC *et al* (2010). Stimulation of medial prefrontal cortex serotonin 2C (5-HT$_{2C}$) receptors attenuates cocaine-seeking behavior. *Neuropsychopharmacol* **35**: 2037–2048.

Schram MJ, Schoedel KA, Barlett C, Shazer RL, Sellers EM (2009). Abuse potential evaluation of lorcaserin, a selective and potent agonist at the serotonin 2C (5-HT$_{2C}$) receptor, in healthy male and female recreational polydrug users. *Amer Coll Neuropsychopharmacol*. 48th Annual Meeting, Hollywood, CA.

Smith SR, Prosser WA, Donahue DJ, Morgan ME, Anderson CM, Shanahan WR *et al* (2009). Lorcaserin (APD356), a selective 5-HT(2C) agonist, reduces body weight in obese men and women. *Obesity (Silver Spring)* **17**: 494–503.