




## RESEARCH HIGHLIGHT

# Impaired cognitive behavioral flexibility following methamphetamine or high caloric diet consumption: a common 5-HT<sub>2C</sub> mechanism?

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Illicit drugs of abuse, such as methamphetamine, can be conceptualized in economic terms as highly purified and potent consumable commodities. The progression from substance abuse to substance use disorder diagnosis involves impaired decision-making processes that results in perseverative behavior directed towards the procurement and use of the abused drug at the expense of other alternative nondrug reinforcers (e.g., job, health, or family interactions) [1]. Perseverative behavior is defined as an inability to change behavior in response to changing reinforcement contingencies that may or may not be signaled to the organism by stimuli. Improved understanding of the behavioral and neurobiological mechanisms of these perseverative behaviors should provide insight into potential pharmacological targets for clinical intervention and treatment.

Similar to drugs of abuse, certain foods (i.e., high fat and/or high sugar) can also be categorized as highly purified and potent consumable commodities. Foods derived from plants, such as apples, contain the sugar fructose along with fiber and other macronutrients and micro-nutrients. However, science has discovered ways to extract sugar from nature and package it into highly purified forms such as high-fructose corn syrup. From an evolutionary standpoint, humans have evolved to defend lower limits of body weight and adiposity; however, the upper limits of body weight and adiposity are poorly defended, especially in our modern society where there is an abundance of palatable, calorically dense food. Although the concept of food “addiction” is still being debated in both the scientific and medical communities [2], there is consensus that despite the procurement and intake of food as a necessary part of survival, there is also an emotional component that involves the reinforcing or pleasurable aspects and that may have some neurobiological and behavioral homology with drugs of abuse and substance use disorder diagnosis [3].

In their recent *Neuropsychopharmacology* article, Perez Diaz et al. [4] propose a novel G protein-coupled receptor target to attenuate increased perseverative behavior in a discrimination reversal learning procedure following long-term methamphetamine self-administration or high caloric diet consumption in nonhuman primates. Perez Diaz et al. [4] initially trained female rhesus monkeys to respond for a food reinforcer (M&Ms, Skittles) during a discrimination reversal learning procedure. Once trained, the subjects underwent a reversal trial where the food reinforcer was hidden under one of the previously unreinforced objects. The role of serotonin (5-HT)<sub>2C</sub> receptor activation on reversal trial performance was then examined before and after either a 6-month history of

intravenous methamphetamine self-administration (0.01 mg/kg per injection) or 6-month history of consuming a high caloric diet (36% fat, 18% protein, 16.4% sugar carbohydrate, and 29.9% fiber–starch carbohydrate). There were three main findings. First, the findings implicate a role of 5-HT<sub>2C</sub> receptors in perseverative errors during the discrimination reversal trial. For example, acute 5-HT<sub>2C</sub> agonist WAY163909 administration increased correct responses and decreased perseverative responses in monkeys before methamphetamine or high caloric diet exposure. Second, a history of methamphetamine self-administration or consumption of a high caloric diet selectively increased the number of perseverative responses without altering the number of correct responses emitted. Lastly, WAY163909 attenuated perseverative responses following both methamphetamine and high caloric diet exposure similar to baseline conditions.

5-HT<sub>2C</sub> agonists (e.g., WAY163909 or lorcaserin) have been mostly investigated in preclinical studies to decrease drug self-administration toward the development of candidate pharmacotherapies for substance use disorder treatment [5, 6]. Clinical trials (NCT03007394; NCT03192995) examining 5-HT<sub>2C</sub> agonists as medications for cocaine use disorder are ongoing to provide critical feedback on preclinical results and on the clinical utility of 5-HT<sub>2C</sub> agonists. 5-HT<sub>2C</sub> receptors are highly expressed on GABAergic neurons in the prefrontal cortex, ventral tegmental area, and ventral striatum (i.e., nucleus accumbens) [5]. These brain regions comprise the mesolimbic dopamine reward pathway that has been implicated in substance abuse, overeating of high caloric foods, and perseverative impairments during discrimination reversal learning procedures [3, 7]. Perez Diaz et al. [4] extend these previous findings by suggesting that 5-HT<sub>2C</sub> activation attenuates methamphetamine-related and high caloric diet-related increases in perseverative responding in a discrimination reversal learning procedure.

Although the findings from Perez Diaz et al. [4] are provocative, the results prompt several questions like any good experiment does. Three will be mentioned. First, if a 5-HT<sub>2C</sub> agonist attenuates perseverative behavior, would a 5-HT<sub>2C</sub> antagonist enhance perseverative behavior? Second, the effectiveness of acute 5-HT<sub>2C</sub> agonist administration on attenuating perseverative responding following the 6-month history of methamphetamine or high caloric diet is intriguing. Current Food and Drug Administration-approved medications for substance use disorders (e.g., buprenorphine) and binge-eating disorders (e.g., lisdexamfetamine) are prescribed based on repeated dosing schedules. Whether acute 5-HT<sub>2C</sub> agonist

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Received: 16 September 2018 Revised: 20 September 2018 Accepted: 25 September 2018  
Published online: 24 October 2018

administration would also be sufficient to reverse perseverative behavior in humans diagnosed with methamphetamine use disorder or binge-eating disorder remains an empirical question. A final intriguing result is that a 6-month history of methamphetamine self-administration increased perseverative responding in the discrimination reversal learning procedure when the reinforcer is not methamphetamine, but a high caloric food (e.g., M&M or Skittle). Why would repeated methamphetamine exposure increase perseverative responding in the discrimination reversal procedure reinforced with food? One potential explanation is that repeated methamphetamine or a high caloric food exposure converge to produce a global impairment in reversal learning regardless of reinforcement contingencies. Future studies could address this using methamphetamine as the reinforcer in the discrimination reversal learning procedure.

Overall, Perez Diaz et al. [4] provide compelling preclinical evidence that 5-HT<sub>2C</sub> activation decreases perseverative behavior regardless of experimental drug or diet history. The use of nonhuman primates as research subjects in the Perez Diaz et al. [4] enhances the potential translatability of these findings to positive clinical outcomes [8]. The current opioid and obesity public health crises has reinvigorated preclinical and clinical research efforts to develop safer and more effective treatment. Improved understanding of the neurobiological and behavioral mechanisms associated with abused drug or high caloric food consumption should unmask novel pharmacotherapy targets to treat human suffering associated with these clinical conditions.

#### FUNDING AND DISCLOSURE

MLB declares that his research has been funded by the National Institutes of Health (NIH). The author declares no competing interests. The content is solely

the responsibility of the author and does not necessarily represent the official views of NIH.

#### ACKNOWLEDGEMENTS

I thank Dr. Yavin Shaham and Dr. Michael Nader for insightful comments on an earlier version of this manuscript.

#### ADDITIONAL INFORMATION

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