



RESEARCH HIGHLIGHT

Taking the scenic route: an endogenous gut lipid messenger curbs binge eating in rats

A research highlight on ‘Oleoylethanolamide decreases frustration stress-induced binge-like eating in female rats: a novel potential treatment for binge eating disorder’ by Romano et al., 2020

Richard M. O'Connor¹

Neuropsychopharmacology (2020) 45:1779–1780; <https://doi.org/10.1038/s41386-020-0722-z>

Pharmacological treatment options for binge eating disorder (BED) remain severely limited with lisdexamfetamine being the only FDA approved drug therapy for BED. While beneficial to many, lisdexamfetamine has a rich pharmacology and affects a wide range of brain systems leading to a significant side-effect burden, which affects compliance [1]. In the current issue of *Neuropsychopharmacology* Romano et al. [2] use oleoylethanolamide (OEA) to access the brain's motivation system through manipulation of gut signaling, perhaps providing a more restrained modulation of brain function and thus limiting undesirable side effects.

OEA is an endogenous lipid messenger found in the small intestine that signals dietary fat intake to the brain through sensory vagal nerve fibers, leading to decreased feeding [3]. Interestingly, the dietary supplement PhosphoLean, which contains the OEA precursor N-oleyl-phosphatidyl-ethanolamine, increases compliance in weight loss programs [4] and reduces impulsivity in young heavy drinkers [5]. Thus, OEA may facilitate enhanced self-control, positing it as a promising therapeutic to help restrain binge eating.

To test this idea Romano et al. used an experimental procedure that led to recurrent rapid binge-like eating episodes in rats that conspicuously resembles the binge eating seen in human subjects with BED [6]. Female rats underwent a thrice repeated cycle of caloric restriction, followed by ad-libitum access to chow with limited temporal access to a highly palatable Nutella mixture. Finally, rats were exposed to a ‘frustration’ stress in which they were initially exposed to the familiar sight and smell of the palatable mixture for 15 min while the actual food itself remained tantalizing out of reach. When granted access for the 2-h test period, the combination of cyclical dietary restraint and stress led to binge-like intake of the palatable mixture with rats consuming on average ~150 Kcal per kg body weight during the first 15 min of access, which was 50% more than their non-bingeing counterparts. OEA delivered 1 h prior (2.5, 5, or 10 mg/kg i.p.) significantly curbed bingeing in a dose-dependent manner yet remarkably, in rats that did not undergo the full diet restriction/stress procedure (and therefore did not show bingeing behavior), left normal hedonic intake of the palatable food mixture intact.

What changes to brain signaling are induced by OEA treatment that might result in this constrained pathological bingeing while

leaving normal hedonic feeding intact? To answer this, Romano et al. used immunohistochemistry to measure expression levels of the immediate early gene c-Fos in response to OEA treatment (10 mg/kg). They detected increased c-fos in the nucleus accumbens (NAc), caudate putamen (CPU), amygdala, and substantia nigra of bingeing rats. OEA decreased this binge eating induced increase, and also increased c-fos levels in the paraventricular nucleus and ventral tegmental area in bingeing rats but not in their control counterparts. To establish how these changes to gene transcription networks might alter neuronal signaling Romano et al. used HPLC to measure the levels of specific neurotransmitters and their metabolites in brain regions key to food motivation. Dopamine signaling in particular is a key mechanism driving the incentive salience of food items and polymorphisms that perturb normal dopaminergic function have been linked to the severity of BED disease pathology [7]. Noradrenaline and serotonin signaling have both previously been linked to OEA derived reductions to depression-like behavior in rodents [8]. Mirroring observations at the behavioral level, OEA profoundly affected the turnover of these neurotransmitters exclusively in bingeing rats while mostly leaving turnover in non-bingeing rats undisturbed.

Obesity-induced impaired gut OEA synthesis has been linked to blunted striatal dopamine signaling that when restored via OEA supplementation rescues obesity-impaired motivational deficits [9]. Having established bingeing rats display altered dopamine metabolism, Romano et al. sought to understand if OEA may be mediating its therapeutic effects on binge eating through gut-mediated changes to striatal dopamine responses. Using microdialysis, the authors found increased dopamine release in the shell subregion of the NAc of bingeing and non-bingeing rats during the test period of the bingeing procedure when the rats were given free access to the palatable food. Remarkably, given previous reports detailing OEA's restoration of normal food hedonics through potentiating dopamine signaling [9], OEA blocked the palatable food-induced rise in dopamine release.

The authors also tested two additional potential therapeutic mechanisms of OEA treatment. Using a combination of immunohistochemistry and in situ hybridization, the authors found that OEA

¹Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
Correspondence: Richard M. O'Connor (richard.oconnor@mssm.edu)

rescued the reduced levels of oxytocin receptor that were found in bingeing rats in the NAc and CPu. In addition, OEA administration decreased levels of corticotropin-releasing factor in central amygdala.

Romano et al. have provided promising data supporting the utility of OEA as a novel therapeutic for BED. However, important questions remain. Although the authors have unveiled a wide array of potential therapeutic mechanisms, a precise mechanism of action was not demonstrated. Future studies, using genetic, pharmacological, chemogenetic, and optogenetic tools, will likely be required to establish causal links between OEA behavioral actions and the reported neurobiological changes. Moreover, given that OEA's role as a brain–gut signaling mechanism was discovered partially due to its effect of suppressing homeostatic feeding in rodents [3] it will be crucial to comprehensively profile the effects of OEA on feeding and reward processes generally to confirm that the apparently beneficial effects of OEA are not secondary to a suppressive action on brain reward function.

Finally, how effective would OEA be in treating BED in a clinical setting? Crucial to OEA's previously established therapeutic effects is its capacity to modulate brain dopamine dynamics [9] and the current paper indicates as much for BED. It will be critical to establish how effective OEA treatment will be for individuals with underlying disruptions to striatal dopamine signaling such as those who carry the Taq1A1 polymorphism and individuals who are obese [10].

To sum, Romano et al. provide evidence suggesting that OEA should be prioritized a promising candidate for the treatment of BED. Its circuitous route to the brain via vagal afferents holds promise that OEA's therapeutic reach will not be restricted by the side effects of currently available therapeutics.

FUNDING AND DISCLOSURE

This work was supported by financial support from a Pfizer sponsored postdoctoral fellowship from the Obesity Society and from the National Institute of Drug Abuse (DA045649). The author has no other disclosures to report.

ADDITIONAL INFORMATION

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Heo YA, Duggan ST. Lisdexamfetamine: a review in binge eating disorder. *CNS Drugs*. 2017;31:1015–22. <https://doi.org/10.1007/s40263-017-0477-1>
2. Romano A, et al. Oleoylethanolamide decreases frustration stress-induced binge-like eating in female rats: a novel potential treatment for binge eating disorder. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2020. <https://doi.org/10.1038/s41386-020-0686-z>
3. Rodriguez de Fonseca F, et al. An anorexic lipid mediator regulated by feeding. *Nature*. 2001;414:209–12. <https://doi.org/10.1038/35102582>
4. Rondanelli M, et al. Administration of a dietary supplement (N-oleyl-phosphatidylethanolamine and epigallocatechin-3-gallate formula) enhances compliance with diet in healthy overweight subjects: a randomized controlled trial. *Br J Nutr*. 2009;101:457–64. <https://doi.org/10.1017/S0007114508024008>
5. van Kooten MJ, Veldhuizen MG, de Araujo IE, O'Malley SS, Small DM. Fatty acid amide supplementation decreases impulsivity in young adult heavy drinkers. *Physiol Behav*. 2016;155:131–40. <https://doi.org/10.1016/j.physbeh.2015.11.032>
6. Cifani C, Polidori C, Melotto S, Ciccocioppo R, Massi M. A preclinical model of binge eating elicited by yo-yo dieting and stressful exposure to food: effect of sibutramine, fluoxetine, topiramate, and midazolam. *Psychopharmacology*. 2009;204:113–25. <https://doi.org/10.1007/s00213-008-1442-y>
7. Bello NT, Hajnal A. Dopamine and binge eating behaviors. *Pharmacol Biochem Behav*. 2010;97:25–33. <https://doi.org/10.1016/j.pbb.2010.04.016>
8. Yu HL, Sun LP, Li MM, Quan ZS. Involvement of norepinephrine and serotonin system in antidepressant-like effects of oleoylethanolamide in the mice models of behavior despair. *Neurosci Lett*. 2015;593:24–28. <https://doi.org/10.1016/j.neulet.2015.03.019>
9. Tellez LA, et al. A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science*. 2013;341:800–2. <https://doi.org/10.1126/science.1239275>
10. Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by Taq1A A1 allele. *Science*. 2008;322:449–52. <https://doi.org/10.1126/science.1161550>