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Editorial

Obesity, Dopamine, and Reward Behaviors

Obesity is now a major health problem in many societies worldwide. In this issue Stankowska and Gjedde have provided an excellent overview of studies of dopamine (DA) neurotransmission in the development of obesity, and propose an innovative hypothesis regarding the evolution of changes in DA neurotransmission with increasing body mass index (BMI). This hypothesis integrates studies of sensation seeking, which is both found at higher levels in the obese and is believed to be a risk factor for obesity, studies of reward sensitivity and studies of DA neurotransmission in obesity. While there are some monogenetic polymorphisms that lead to obesity, the overwhelming majority of cases of human obesity appear to result from the interaction of polygenetic predispositions to obesity with an environment in which highly palatable food is readily available (1–4). The excessive consumption of highly palatable foods is mediated by their rewarding properties (5–7). DA neurotransmission in the brain reward circuit, particularly the ventral striatum/nucleus accumbens, plays an important role in regulating reward behaviours (8,9). In addition, DA neurotransmission in the dorsal striatum is required for normal eating behaviours and has a permissive role in eating behaviours (10). The importance of DA neurotransmission in the consumption of highly palatable foods has resulted in numerous animal studies of DA neurotransmission in the development of obesity as well as a number of studies of human brain function in obesity, but relatively few studies that directly examine DA neurotransmission in humans with the development of obesity.

There have been two theories regarding the changes in DA neurotransmission that predispose to the development of obesity. The first postulates a reward deficient state that leads to compensatory overeating to remedy an anhedonic state; decreased DA neurotransmission in the brain reward circuit is hypothesised to be a significant factor in the reward deficient state leading to obesity (11,12). Consistent with this hypothesis are the findings of decreased striatal DA D2 receptor levels in the dorsal striatum in extremely obese human subjects (BMI $>$ 45), and animal models of diet-induced obesity that consistently demonstrate decreased ventral striatal/nucleus accumbens DA release and DA D2 receptor levels (13–18). The development of compulsive food ingestion in animals has been related to the development of decreased striatal DA D2 receptor levels in the setting of decreased DA release and elevated reward thresholds (18). These changes are similar to those seen in alcohol and drug abuse which are characterised by decreased DA release, decreased striatal/ventral DA D2 receptor levels, and anhedonia (19–25). This has led to the concept of obesity being a food addiction (26,27). The second hypothesis postulates that in individuals prone to obesity there is an increased behavioural salience of highly palatable foods resulting in increased intake of these foods leading to obesity. The increased behavioural salience of food, that is food wanting, is postulated to be mediated by increased ventral striatal/nucleus accumbens DA release in response to highly palatable food stimuli (9, 28, 29). Consistent with this hypothesis are (a) fMRI studies showing greater food related activation in the brain reward circuit both in subjects at high risk for obesity and obese individuals (30–36), (b) a strong correlation between food cue activation and individual differences in reward drive (37) (c) the role of brain reward circuit DA neurotransmission in food motivation and food seeking energy expenditure (38), and (d) a recent study suggesting increased DA release in binge eating disorder (39).

Higher levels of sensation/novelty seeking behaviour are seen in obese as well as in substance abusing subjects. Sensation/novelty seeking as well as impulsivity appear to be personality traits that predispose to both obesity and substance abuse (40,41). In humans both sensation/novelty seeking and impulsivity are mediated by DA neurotransmission (42–45). Gjedde has recently reported an inverted 'U' shaped relationship between sensation seeking and striatal DA D2 receptor levels in healthy subjects (46). This inverted 'U' shaped relationship is believed to reflect higher occupancies of DA D2 receptors by endogenous DA at either end of this curve. A similar inverted parabolic relationship has been reported between reward sensitivity and BMI (47,48). Stankowska suggests that both the relationships of BMI to reward sensitivity and sensation seeking to

available striatal DA D2 receptor levels reflect a common aetiology that is related to the evolution of DA neurotransmission with the development of obesity. Such an evolution moves beyond the static concepts of reward deficiency or increased behavioural salience that have previously been proposed as risk factors for obesity. The postulated evolution proposes that at low BMI's, that is BMI's of 18 or less, there are decreased extracellular DA levels along with relatively larger decreases in total levels of DA D2 receptors leading to fewer available DA D2 receptors consistent with animal studies (49). The decreased extracellular DA levels are believed to mediate the lower levels of sensation seeking on the left hand side of the curve of sensation seeking versus DA D2 receptors while the decreased available DA D2 receptor levels are hypothesised to mediate the decreased reward sensitivity seen at underweight BMI's. Normal weight to perhaps mildly obese subjects, BMI's of 19 up to the low 30's, in comparison to underweight subjects are postulated to have the highest levels of available DA D2 receptors due to relatively greater increases in total DA D2 receptor levels than extracellular DA; the greater reward sensitivity in these subjects is hypothesised to be due to the higher levels of available DA D2 receptors while the increased DA release is associated with increased sensation seeking. As BMI increases above 35, further increases in both extracellular DA and total DA D2 receptors are postulated to occur. However, a greater increase is believed to occur in extracellular DA levels than in DA D2 receptor levels producing decreased available DA D2 receptor levels; decreased available striatal DA D2 receptor levels have been reported in very obese humans consistent with this hypothesis (13,14). The decreased available DA D2 receptor levels in moderately to severely obese subjects is believed to account for the decreased reward sensitivity while the increased DA release is hypothesised to mediate the high levels of sensation seeking seen in these subjects.

However, Stankowska acknowledges that, given the paucity of human studies of DA neurotransmission in obesity, alternative explanations are possible. Many of the proposed changes in DA neurotransmission in obesity in Stankowska's review are based on Gjedde's study of sensation seeking and DA D2 receptor levels in healthy subjects (46). The BMI of the subjects studied in Gjedde's study is not stated. While Gjedde's findings in healthy subjects may be accurate in describing the relationship between sensation seeking and DA D2 receptor levels in healthy, nonobese subjects, there may be changes in the relationship of DA neurotransmission to reward-related behaviours in individuals who are very obese or significantly underweight.

As discussed above, Stankowska proposes that total striatal DA D2 levels and extracellular DA levels are increased in very obese human subjects. While no studies of baseline extracellular DA levels and total DA D2 receptor levels, which would require PET studies of DA D2 receptors before and following DA depletion, have been reported in obese humans, animal studies have shown decreased baseline extracellular DA levels, decreased amphetamine induced DA release, and decreased absolute levels of DA D2 receptor levels in obese animals, particularly in those who compulsively consume food (16–18). Both Stankowska and other investigators have postulated that extreme obesity may be due to a food addiction and that extremely obese humans may have changes in DA neurotransmission similar to those seen in substance abuse (26,27,50). Studies in human substance abusers have shown both decreased extracellular DA levels, and total DA D2 receptor levels as well as decreased psychostimulant induced DA release and available DA D2 receptor levels (21–25). The limited available data would suggest decreased rather than increased extracellular DA levels and total DA D2 receptor levels in the extremely obese.

While acknowledging that 'the changes in dopaminergic neurotransmission in mild to moderate obesity are unclear', Stankowska proposes that extracellular DA levels, available and total DA D2 receptor levels increase as BMI's increase from an underweight range, that is 18 or under, up to at least a normal to overweight level and possibly extending into the mildly obese range, that is BMI's of 30–35. While no studies of baseline receptor occupancy by extracellular DA versus BMI have been published, we have presented preliminary data regarding D-amphetamine induced DA release in 16 healthy subjects with BMI's ranging from 19 to 35 – low normal to mildly obese (51). Positive correlations of BMI with DA release were seen in all regions except the right temporal cortex ($r = -0.17$) with significant positive correlations seen in the right putamen ($r = 0.581$, $p = 0.023$) and in the left substantia nigra ($r = 0.568$, $p = 0.027$). These results are consistent with increased extracellular DA levels with increasing BMI's from 19 to 35 and are consistent with Stankowska's model. In regard to available DA D2 receptor levels, Haltia reported no change in striatal DA D2/3 receptor levels in overweight and mildly obese subjects (mean BMI = 33, BMI > 27) compared with normal weight subjects (mean BMI = 22, BMI < 24) (52). We have recently presented data consistent with the Haltia study showing nonsignificant decreases, rather than increases, in available DA D2 levels in striatal and most extrastriatal regions over a BMI range of 19–35 in 34 healthy subjects (51).

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These results, while preliminary, suggest increasing extracellular DA levels as BMI's rise from underweight to mildly obese levels, but with little change in available DA D2 receptor levels.

Although the evolution of changes in DA neurotransmission occurring with the development of obesity are not completely understood at present, the limited available studies in humans do suggest that significant changes in DA neurotransmission occur (13,14,51,52). There are very few studies of the factor(s) mediating changes in DA neurotransmission with increasing BMI in humans. While the DA transporter is an important regulator of extracellular DA levels, a recent study has shown no correlation of BMI with DA transporter levels in humans (53). Altered enteric hormone regulation of DA neuronal function in the brain reward circuit with the development of obesity has been demonstrated in animals and recently a single study reporting significant correlations of cerebral DA D2 receptor levels with enteric hormone levels has in humans has been published (54–57). Obesity induced changes in enteric hormone regulation of cerebral DA neurotransmission appear to be a potentially important factors in mediating altered DA neurotransmission and altered reward behaviours with the development of obesity.

In summary, the excellent review of Stankowska and Gjedde puts forth an important hypothesis regarding the evolution of DA neurotransmission in the development of obesity and the role that such changes in DA neurotransmission produce in reward-related behaviours, particularly sensation seeking, in predisposing to the development of obesity. As noted by the authors, alternative hypotheses are possible given the paucity studies of DA neurotransmsion in humans with the development of obesity. There are numerous animal studies which demonstrate that DA neurotransmission plays a critical role in the development of obesity related to increased highly palatable food ingestion. However, we are at a relatively early stage in delineating the nature of such changes in humans and the factor(s) that drive these changes.

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References

1. Mutch DM, Clément K. Unraveling the genetics of human obesity. PLoS Genet 2006;**2**:e188.
2. Goldstone AP, Beales PL. Genetic obesity syndromes. Front Horm Res 2008;**36**:37–60.
3. Walley AJ, Asher JE, Froguel P. The genetic contribution to non-syndromic human obesity. Nat Rev Genet 2009; **10**:431–442.
4. Blakemore AI, Froguel P. Investigation of Mendelian forms of obesity holds out the prospect of personalized medicine. Ann N Y Acad Sci 2010;**1214**:180–189.
5. Mela DJ. Determinants of food choice: relationships with obesity and weight control. Obes Res 2001; (Suppl. 4): 249S–255S.
6. Hetherington MM. Cues to overeat: psychological factors influencing overconsumption. Proc Nutr Soc 2007;**66**:113–123.
7. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. Diabetes 2008;**57**:1768–1773.
8. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 2010;**35**:4–26.
9. Wise RA. Dual roles of dopamine in food and drug seeking: the drive-reward paradox. Biol Psychiatry 2013;**73**:819–826.
10. Palmiter RD. Dopamine signaling in the dorsal striatum is essential for motivated behaviors: lessons from dopamine-deficient mice. Ann N Y Acad Sci 2008;**1129**:35–46.
11. Blum K, Braverman ER, Holder JM et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 2000;**32**(Suppl. i–iv):1–112.
12. Blum K, Liu Y, Shriner R, Gold MS. Reward circuitry dopaminergic activation regulates food and drug craving behavior. Curr Pharm Des 2011;**17**:1158–1167.
13. Wang GJ, Volkow ND, Logan J et al. Brain dopamine and obesity. Lancet 2001;**357**:354–357.
14. de Weijer BA, van de Giessen E, van Amelsvoort TA et al. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. EJNMMI Res 2011;**16**:37.
15. Davis JF, Tracy AL, Schurdak JD et al. Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. Behav Neurosci 2008;**122**:1257–1263.
16. Geiger BM, Behr GG, Frank LE et al. Evidence for defective mesolimbic dopamine exocytosis in obesity-prone rats. FASEB J 2008;**22**:2740–2746.
17. Geiger BM, Haburcak M, Avena NM, Moyer MC, Hoebel BG, Pothos EN. Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. Neuroscience 2009;**159**:1193–1199.
18. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 2010;**13**:635–641.
19. Leventhal AM, Brightman M, Ameringer KJ et al. Anhedonia associated with stimulant use and dependence in a population-based sample of American adults. Exp Clin Psychopharmacol 2010;**18**:562–569.
20. Hatzigiakoumis DS, Martinotti G, Giannantonio MD, Janiri L. Anhedonia and substance dependence: clinical correlates and treatment options. Front Psychiatry 2011;**17**:2–10.
21. Martinez D, Gil R, Slifstein M et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biol Psychiatry 2005;**58**:779–786.
22. Martinez D, Greene K, Broft A et al. Lower level of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D(2)/D(3) receptors following acute dopamine depletion. Am J Psychiatry 2009;**166**:1170–1177.

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23. Martinez D, Saccone PA, Liu F et al. Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. Biol Psychiatry 2012;**71**:192–198.
24. Volkow ND, Wang GJ, Fowler JS et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 1997;**386**:830–833.
25. Volkow ND, Chang L, Wang GJ et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry 2001;**158**:2015–2021.
26. Gearhardt AN, Corbin WR, Brownell KD. Food addiction: an examination of the diagnostic criteria for dependence. J Addict Med 2009;**3**:1–7.
27. Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. Biol Psychiatry 2013;**73**:811–818.
28. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol 2009;**9**:65–73.
29. Smith KS, Berridge KC, Aldridge JW. Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. Proc Natl Acad Sci USA 2011;**27**:E255–E264.
30. Stoeckel LE, Weller RE, Cook EW III, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 2008;**41**:636–647.
31. Del Parigi A, Gautier JF, Chen K et al. Neuroimaging and obesity: mapping the brain responses to hunger and satiation in humans using positron emission tomography. Ann N Y Acad Sci 2002;**967**:389–397.
32. Del Parigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA. Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. Neuroimage 2005;**24**:436–443.
33. O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ. Neural responses during anticipation of a primary taste reward. Neuron 2002;**33**:815–826.
34. Rothemund Y, Preuschhof C, Bohner G et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage 2007;**37**:410–421.
35. 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**:449–452.
36. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci 2011;**31**:4360–4366.
37. Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, Calder AJ. Individual differences in reward drive predict neural responses to images of food. J Neurosci 2006;**26**:5160–5166.
38. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl) 2007;**191**:461–482.
39. Wang GJ, Geliebter A, Volkow ND et al. Enhanced striatal dopamine release during food stimulation in binge eating disorder. Obesity (Silver Spring) 2011;**19**:1601–1608.
40. Sullivan S, Cloninger CR, Przybeck TR, Klein S. Personality characteristics in obesity and relationship with successful weight loss. Int J Obes 2007;**4**:669–674.
41. Jupp B, Dalley JW. Behavioral endophenotypes of drug addiction: Etiological insights from neuroimaging studies. Neuropharmacology 2013, Jun 10. doi:pii: S0028-3908(13)00255-4. 10.1016/j.neuropharm.2013.05.041. Epub ahead of print.
42. Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. Neuropsychopharmacology 2002;**27**:1027–1035.
43. Riccardi P, Zald D, Li R et al. Sex differences in amphetamine-induced displacement of [(18)F]fallypride in striatal and extrastriatal regions: a PET study. Am J Psychiatry 2006;**163**:1639–1641.
44. Zald DH, Cowan RL, Riccardi P et al. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J Neurosci 2008;**28**:14372–14378.
45. Buckholtz JW, Treadway MT, Cowan RL et al. Dopaminergic network differences in human impulsivity. Science 2010;**329**:532.
46. Gjedde A, Kumakura Y, Cumming P, Linnet J, Møller A. Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. Proc Natl Acad Sci USA 2010;**107**:3870–3875.
47. Davis C, Fox J. Sensitivity to reward and body mass index (BMI): evidence for a non-linear relationship. Appetite 2008;**50**:43–49.
48. Verbeken S, Braet C, Lammertyn J, Goossens L, Moens E. How is reward sensitivity related to bodyweight in children? Appetite 2012;**58**:478–483.
49. Pothos EN, Creese I, Hoebel BG. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. J Neurosci 1995;**15**:6640–6650.
50. Everitt BJ, Robbins TW. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci Biobehav Rev 2013, Feb 21. Epub ahead of print.
51. Kessler R, Zald D, Ansari MS, Li R, Cowan R. Regional dopamine release and dopamine D2 receptor levels in normal weight, overweight, and mildly obese subjects. J Cerebr Blood Flow and Metab 2012;**32**(Suppl. 1):S88–S89.
52. Haltia LT, Rinne JO, Merisaari H et al. Effects of intravenous glucose on dopaminergic function in the human brain in vivo. Synapse 2007;**61**:748–756.
53. van de Giessen E, Hesse S, Caan MW, Zientek F, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Guignard R, Akdemir UO, Knudsen GM, Nobili F, Pagani M, Vander Borght T, Van Laere K, Varrone A, Tatsch K, Booij J, Sabri O. No association between striatal dopamine transporter binding and body mass index: a multi-center European study in healthy volunteers. Neuroimage 2013;**64**:61–67.
54. Figlewicz DP, Benoit SC. Insulin, leptin, and food reward: update 2008. Am J Physiol Regul Integr Comp Physiol 2009;**296**:R9–R19.
55. Davis JF, Choi DL, Schurdak JD et al. Leptin regulates energy balance and motivation through action at distinct neural circuits. Biol Psychiatry 2011;**7**:668–674.
56. Morris JK, Bomhoff GL, Gorres BK et al. Insulin resistance impairs nigrostriatal dopamine function. Exp Neurol 2011;**231**:171–180.
57. Dunn JP, Kessler RM, Feurer ID et al. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. Diabetes Care 2012;**35**:1105–1111.