Dopamine signaling in food addiction: role of dopamine D2 receptors
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Dopamine (DA) regulates emotional and motivational behavior through the mesolimbic dopaminergic pathway. Changes in DA signaling in mesolimbic neurotransmission are widely believed to modify reward-related behaviors and are therefore closely associated with drug addiction. Recent evidence now suggests that as with drug addiction, obesity with compulsive eating behaviors involves reward circuitry of the brain, particularly the circuitry involving dopaminergic neural substrates. Increasing amounts of data from human imaging studies, together with genetic analysis, have demonstrated that obese people and drug addicts tend to show altered expression of DA D2 receptors in specific brain areas, and that similar brain areas are activated by food-related and drug-related cues. This review focuses on the functions of the DA system, with specific focus on the physiological interpretation and the role of DA D2 receptor signaling in food addiction. [BMB Reports 2013; 46(11): 519-526]

INTRODUCTION
Catecholamines have often been linked to the behavioral pathology of a number of neurological and psychiatric disorders such as Parkinson’s disease, Huntington’s disease, drug addiction, depression, and schizophrenia. Dopamine (DA) is the predominant catecholamine in the brain and is synthesized by mesencephalic neurons in the substantia nigra (SN) and the ventral tegmental area (VTA). DA neurons project from the SN and VTA to many different areas of the brain. These dopaminergic cell groups are designated as group ‘A’ cells, indicating aminergic DA-containing cells, and are subdivided into cell groups A8 through A14. DA cells within the pars compacta (A8) and neighboring areas (group A9) of the SN project to the basal ganglia (striatum, globus pallidus, and subthalamic nucleus). This projection constitutes the nigrostriatal pathway, which is involved primarily in the control of voluntary movement but also in goal-directed behaviors (Fig. 1). From the VTA, A10 cell group projects to the nucleus accumbens (NAc), prefrontal cortex, and other limbic areas. Thus, this group of cells is termed the mesolimbic and mesocortical pathways (Fig. 1). These neurons play a crucial role in reward-related behaviors and motivation. Another distinct group of cells constitutes the tubero-infundibular pathway. These cells arise from the arcuate nucleus (cell group A12) and periventricular nucleus (cell group A14) of the hypothalamus and project to the pituitary. This pathway is known to control the release and synthesis of pituitary hormone, primarily prolactin (1-4).

Invited Mini Review
Regulation of the DA system for reward-related behaviors is mediated by the mesolimbic and mesocortical pathways. The role of DA in reward-related behaviors has received much attention because of severe consequences of dysfunction within the mesolimbic and mesocortical circuits, which include drug addiction and depression. It has recently become accepted that DA-mediated food reward is linked to obesity, a major public health problem.

It is well known that a homeostatic regulation center for feeding behaviors exists in the brain, in particular the hypothalamus, and serves to integrate different hormonal and neuronal signals that control appetite and energy homeostasis in controlling body weight. This homeostatic regulation of body weight monitors the level of body adiposity by employing different regulators such as leptin, insulin, and ghrelin (5). However, the motivation for food is strongly associated with reward, and responding to the hedonic properties of food such as its sight, smell, and taste may be associated with conditioning cues. These hedonic qualities can override the homeostatic system (6). Therefore, delineating how this food reward circuit in the brain can control appetite and eating behaviors in connection with the brain’s homeostatic system of energy balance is difficult.

Considerable evidence suggests that synaptic modifications of the mesolimbic DA system are critically associated with the rewarding effects of drugs of abuse as well as with food reward (7-9). However, DA reward signaling is far more complex than it appears, and it is also implicated in learning and conditioning processes, as evidenced by studies revealing that dopaminergic reward signals are involved in coding for reward prediction error in behavioral learning (10-13). In drug addiction, it is well known that the rewarding effects of drugs are primarily induced by increased DA release upon targeting of a specific substrate, such as the DA transporter in the case of cocaine. In food addiction, however, it remains to be elucidated how food reward can activate the DA reward signal in a manner similar to that evoked by drug addiction. It is important to understand the mechanisms by which these reward components induce adaptive changes in DA circuitry responsible for these addictive behaviors (7-9).

In this review, I will provide a short summary of dopaminergic signaling in food reward-related behaviors, with a focus on recent studies on the role of DA receptor subtypes, in particular D2 receptors, in this process.

**DA D2 RECEPTORS**

DA interacts with membrane receptors belonging to a family of seven transmembrane domain G-protein-coupled receptors. This leads to the formation of second messengers and the activation or repression of specific signaling pathways. To date, five different subtypes of DA receptor have been cloned from different species. A general subdivision into two groups has been made based on their structural and G-protein coupling properties: the D1-like receptors, which stimulate intracellular cAMP levels and comprising D1 (14, 15) and D5 (16, 17) receptors, and the D2-like receptors, which inhibit intracellular cAMP levels and comprise the D2 (18, 19), D3 (20), and D4 (21) receptors.

D1 and D2 receptors are the most abundant DA receptors in the brain. The expression of D3, D4, and D5 receptors in the brain is considerably more restricted and weaker than that of D1 and D2 receptors. The D2 receptor is represented by two isoforms generated by alternative splicing of the same gene (18, 22). These isoforms, namely D2L and D2S, are identical except for an insert of 29 amino acids present in the putative third intracellular loop of D2L, which is in fact encoded by exon 6 of the D2 receptor gene, an intracellular domain thought to have a role in coupling this class of receptor to particular second messengers. The large isoform appears to be the predominant form present in all brain regions, although the exact ratio of the two isoforms can vary (22). In fact, the phenotype of D2 receptor total knockout mice was revealed as being quite different from the D2L knockout mice (23-25), indicating that these two isoforms of D2 receptor might have different functions in vivo. Recent results from Moyer and coworkers support a differential in vivo function of the two D2 receptor isoforms in the human brain. They demonstrated that the two variants of the D2 receptor gene (Drd2), caused by D2 receptor alternative splicing, possessed intronic single-nucleotide polymorphisms (SNPs) that were differentially associated with cocaine abuse in Caucasians (26, 27). D2S and D2L mRNA levels were measured in tissues from human brain autopsies (prefrontal cortex and putamen) obtained from cocaine abusers and controls, and the relationship between the D2 receptor gene genotype, D2SL splicing, and cocaine abuse was examined. The results supported a robust effect of difference of specific SNPs in decreasing the relative expression of D2S in humans, representing strong risk factors in cases of cocaine overdose (26). Given that these two isoforms are generated by alternative splicing of a single gene, it would also be interesting to see whether the ratio of the two isoforms could be a factor contributing to such disease.

D2 receptors are also localized presynaptically, as indicated by experiments examining receptor expression and binding sites in DA neurons throughout the midbrain (28). These D2 autoreceptors may either be somatodendritic autoreceptors, which are known to decrease neuronal excitability (29, 30), or terminal autoreceptors, which mostly reduce DA synthesis and packaging (31, 32) and inhibit DA release (33-35). It has been suggested that in the embryonic stage, the D2 autoreceptor may play a role in DA neuronal development (36-38).

Bello and coworkers recently generated mice conditionally deficient for the D2 receptor in midbrain DA neurons (referred to as autoDrd2KO mice). These autoDrd2KO mice lacked DA-mediated somatodendritic synaptic responses and inhibition of DA release (39) and displayed elevated DA synthesis and release, hyperlocomotion, and supersensitivity to...