Mesolimbic dopamine in obesity and diabetes

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Monoaminergic neurotransmitter dopamine plays a critical role in various vital functions including hormonal regulation, reward, emotions and food intake. Multiple aspects of food intake that include food selection, satiety and energy expenditure could be modulated by changes in central dopaminergic transmission (1,2). Several lines of research indicate that abnormal dopaminergic neurotransmission could be involved in pathophysiological processes leading to obesity. Most of these studies are focused on the hypothalamic dopamine transmission that is believed to play a pivotal role in the guidance of fuel flux and energy homeostasis (3). Generally, these investigations have indicated a decreased dopaminergic signaling in obese subjects (3). For example, dopamine D2 receptors were found to be lower in several brain regions in both obese experimental animals and humans and it has been observed that dopamine D2 agonist bromocriptine can exert favorable metabolic changes in seasonal obesity (3). In line with this contention, obesity is one of the best known side-effect of antipsychotic drugs that exert their actions mostly via antagonism of D2 dopamine receptors (4). It should be noted, however, that there is also evidence indicating that in brain mesolimbic structures responsible for motivation, reward and emotions, particularly in the nucleus accumbens, a situation may be completely different and obesity can be accompanied with an increased dopamine signaling that could determine an increased motivation for food consumption (5). It has become increasingly clear that food shares the ability of many drugs of abuse to activate common reward circuits such
as mesolimbic dopamine system. Furthermore, obesity, like drug addiction, could be considered as a special case of the consequences of ingestive behavior gone awry (2,6).

In this issue of *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*, Anderzhanova et al. (7) present novel and interesting observations on the altered basal and stimulated dopamine release in the nucleus accumbens of obese OLETF rats as a function of age and diabetic status. Particularly, by using a quantitative microdialysis in vivo approach, it has been convincingly demonstrated that obese OLETF rats have increased stimulated dopamine release and uptake in the nucleus accumbens in age-dependent manner. Microdialysis procedures are based on the implantation of microdialysis probes into specific tissues or brain regions of animals and collection of perfusates for subsequent analysis (8). This technique has a wide use in studies aimed to understand brain neurochemistry in vivo because it provides a reliable assessment of the extracellular levels of neurotransmitters at basal conditions at low nanomolar range. Microdialysis probes are located relatively far from release sites and the concentrations measured most likely represent extrasynaptic neurotransmitter levels which are, nonetheless, well reflective of neuronal activity and synaptic release (8). Since at various pathological conditions neurotransmitter synthesis, storage, release or metabolism can be unpredictably changed it is becoming critical to determine basal extracellular levels of a given neurotransmitter in a certain brain area. Conventional microdialysis is commonly used to assess relative changes in neurotransmitter levels in response to stimuli or drug challenge, but due to multiple technical problems related to microdialysis probe recovery in rapidly changing tissue conditions *in vivo*, this approach does not allow reliable estimations of basal extracellular levels of neurotransmitters (9,10). Two major quantitative approaches were developed to measure “true” extracellular level of a neurotransmitter: "no net flux" and "low perfusion rate"
microdialysis (9,10). In one of these approaches, the “no net flux” method, the infusion of several concentrations of the studied neurotransmitter (i.e. dopamine) is performed to determine the concentration where no net transfer of neurotransmitter over the microdialysis membrane occurs. This allows the direct determination of the extracellular concentration of a neurotransmitter. Furthermore, this analysis provides the estimation of the extraction fraction index that could be defined also as relative recovery in vivo and reflect indirectly the activity of plasma membrane transporter mediated uptake of neurotransmitter (11,12). Generally, prior to assessment of responses to pharmacological or physiological stimuli in animals, a reliable determination of basal extracellular levels of neurotransmitters by quantitative approaches is strongly recommended (9-12).

In this report (7), such careful microdialysis study was performed in obese OLETF rats to evaluate the status of mesolimbic dopaminergic transmission in obesity. The OLETF rats have a mutation in cholecystokinin-1 (CCK-1) receptor due to spontaneous deletion spanning the region from promoter to second exon of the CCK receptor gene. Due to lack of activity in this receptor, believed to be critical for action of CCK on satiety, the rats have a reduced satiety, an increased meal size, increased sensitivity to food reward and gradually become obese and develop type-2 diabetes (13,14). In the present study (7), hyperphagia-related obese OLETF rats were analyzed at different age groups reflecting non-diabetic, pre-diabetic and diabetic status. It has been observed that the basal extracellular levels of dopamine are increased in young obese-prone rats that likely contribute to the increased rewarding value and intake of food in these subjects. While similar trend was observed also in pre-diabetic rats, at later stages no significant difference between obese and control rats were observed. Nevertheless, an increased potassium-evoked dopamine release was noted in all groups with maximal difference observed in aged
group displaying diabetic status. At the same time, analysis of extraction fraction values indicated an increase in dopamine uptake in older rats that could potentially explain why increased release capacity in aged rats does not manifest as an increase in basal extracellular concentrations of dopamine. Based on the well established modulatory role of CCK over central dopaminergic transmission (15), it is proposed that these changes may be reflective of CCK-1 deficiency-related dysregulation of accumbens dopamine dynamics (7). The finding of significantly elevated basal extracellular dopamine levels in the nucleus accumbens of young non-diabetic rats is particularly intriguing. Since increased dopamine tone in mesolimbic brain areas is generally leads to an increased hedonic value of various rewarding stimuli including food (2,6,16), this fact may determine an increased motivation for food consumption in these animals that eventually, at later stages, could lead to obesity and deficits in glucose control.

Taken together, these data provide important novel information for understanding the relationship between mesolimbic dopamine and obesity and provide further support for the view that abnormal food intake shares the same neurochemical mechanisms with drug addiction (2,6).

While these investigations provide solid support for an increased dopamine transmission in the nucleus accumbens of OLETF rats, it should be noted that these experiments were performed in anesthetized rats. Anesthesia is known to affect several processes critical for normal dopamine release and it is a preferred practice that microdialysis experiments in vivo are carried out in non-anesthetized, freely-moving animals (8). This potentially could explain the fact that age-dependent decreases in basal dopamine levels in both OLETF and control rats were somewhat more dramatic that could be expected. Further studies in freely-moving animals will be necessary to validate the present findings in a more physiologically relevant setting. Again, as discussed above, it would be of great interest to test the status of hypothalamic dopamine
neurotransmission in this model of obesity. It is well possible that the extracellular dopamine
dynamics could be changed in a different manner in this brain area. Another brain area that
would be of interest to analyze is the prefrontal cortex where significant abnormalities were
documented in obese subjects presented with food-related stimuli (17). Dopamine is known to
play important role in cortical networks and processes governing decision making might be
altered in this model of hyperphagia-related obesity.

Clearly, this study is just the starting point to understand mechanistically the role of
mesolimbic dopamine-related processes in the aberrant food intake-induced obesity and related
diabetes. Deciphering the multifaceted role of dopamine in these processes could provide a
better understanding of obesity-related events and lead to novel approaches for the treatment of
obesity and related homeostatic dysregulation such as diabetes.

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