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Role of the striatal dopamine, GABA and opioid systems in mediating feeding and fat intake

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HIGHLIGHTS

- Dopamine, GABA, and opioids are key neurotransmitters important for feeding behaviors.
- Palatable food consumption changes dopamine, dopamine receptors and transporters in the striatum
- GABA stimulation **in the striatal complex** promotes general feeding.
- Opioids stimulation **in the striatal complex** promotes palatable feeding.

ABSTRACT

Food intake, which is a highly reinforcing behavior, provides nutrients required for survival in all animals. However, when fat and sugars consumption goes beyond the daily needs, it can favor obesity. The prevalence and severity of this health problem has been increasing with time. Besides covering nutrient and energy needs, food and in particular its highly palatable components, such as fats, also induce feelings of joy and pleasure. Experimental evidence supports a role of the striatal complex and of the mesolimbic dopamine system in both feeding and food-related reward processing, with the nucleus accumbens as a key target for reward or reinforcing-associated signaling during food intake behavior. In this review, we provide insights concerning the impact of feeding, including fat intake, on different types of receptors and neurotransmitters present in the striatal complex. Reciprocally, we also cover the evidence for a modulation of palatable food intake by different neurochemical systems in the striatal complex and in particular the nucleus accumbens, with a focus on dopamine, GABA and the opioid system.

Keywords: Dopamine, Opioids, GABA, Obesity, Palatable food, Nucleus accumbens

In the present time, overeating is a significant problem, which is favored by the easy availability and cheaper price of palatable junk food, enriched in fats and/or sugar, with little dietary fibers or other important forms of nutritional value (Grotto and Zied, 2010; Myles, 2014). The availability and overconsumption of such palatable foods are contributing factor to overweight, obesity and related metabolic disorders (Johnson and Wardle, 2014; Reichelt and Rank, 2017). Among the brain regions controlling feeding behavior, the hypothalamus is a key brain region important for both feeding and maintaining the energy balance (Ahima and Antwi, 2008; Luquet et al., 2019; Myers et al., 2014; Stuber and Wise, 2016). Many other brain regions, however, also contribute to the various aspects of food intake, such as food choice, motivation, consummatory behavior and satiety. Among these regions, the forebrain striatal complex is a contributor to feeding and related reward processing (Ferrario et al., 2016). The striatal complex, with its dorsal and ventral components, is the input nucleus of the basal ganglia and is involved in various functions from the control of motor functions to goal-directed behaviors. The dorsal striatum in rodents is often divided into a dorsomedial striatum and a dorsolateral striatum, which are roughly analogous to the caudate nucleus and the putamen in primates and humans in which the internal capsule (poorly developed in rodents) does anatomically separate the two structures (Haber, 2016). The dorsomedial striatum has been mostly implicated in goal-directed action, learning and performance, while the dorsolateral striatum has been involved in habit and skill learning (Balleine et al., 2007; Yin et al., 2004, 2006; Yin et al., 2005). The term “ventral striatum” traditionally includes the nucleus accumbens and the olfactory tubercle. Ventrally located in the telencephalon (Park et al., 2019), the nucleus accumbens has been proposed as an interface from motivation to action (Mogenson et al., 1980), and mostly studied for its implication in reward, motivational salience, reinforcement, and in psychopathologies impacting motivation and reward, such as addiction (Di Chiara et al., 2004; Koob and Volkow, 2016; Wise and Robble, 2020) and depression (Francis and Lobo, 2017; Knowland and Lim, 2018; Nestler et al., 2002). The nucleus accumbens is in fact heterogeneous (Castro and Bruchas, 2019; Park et al., 2019), likely including a mosaic of subregions with specific neurochemical and/or connectivity features (Groenewegen et al., 1991; Heimer et al., 1997; Jongen-R elo et al., 1993; Pennartz et al., 1994). However, this complex compartmental organization is often too challenging to consider in

experimental studies, and the nucleus accumbens has been mostly studied either as a whole or through its two main subregions, the core of the nucleus accumbens around the anterior commissure and the shell of the nucleus accumbens surrounding it (Záborszky et al., 1985; Zahm, 1999), with some mediolateral and/or anteroposterior aspects that can also be taken into consideration.

The striatum **includes** five major **neuronal** cell types: two major types of projection neurons, known as medium spiny neurons (MSNs) and three main types of interneurons. The projecting neurons are GABAergic and can be divided into D₁ receptor-expressing MSNs (D1-MSNs) and D₂ receptor-expressing MSNs (D2-MSNs) based on the main dopamine receptors they express, although a small subset of neurons (<5%) have both D₁ and D₂ receptors (Gangarossa et al., 2013a; Gangarossa et al., 2013b; Gerfen and Bolam, 2016; Oorschot, 2016; Oude Ophuis et al., 2014). The three main types of interneurons express either parvalbumin, somatostatin or acetylcholine. Based upon different cell types in terms of neurotransmitters, receptors and connectivity, a highly **organized** system **has been historically proposed to separate dorsal striatum** MSNs into a direct and an indirect projecting pathway (Oorschot, 2016) (**Figure 1A**). **Classically, the** direct pathway **included** MSNs expressing the dopamine D₁ receptors, dynorphin and substance P, while the indirect pathway **included** MSNs mostly expressing dopamine D₂ receptors, enkephalin and adenosine 2A receptors (A_{2A}) (Gerfen and Bolam, 2016; Oorschot, 2016). **While this nomenclature is widely shared for the dorsal striatum, results from the past decades concerning the nucleus accumbens highlighted a more complex organization (Figure 1B), and suggest that the direct and indirect pathways of the nucleus accumbens are not coded by MSN cell types (Kupchik et al., 2015; Kupchik and Kalivas, 2017). Based on neurochemical markers, the striatal complex and its MSNs populations have also been divided into patch/striosome and matrix compartments (Gerfen and Bolam, 2016); (Crittenden and Graybiel, 2016). Notably, the mu opioid receptor, which is greatly enriched in the patch compartment, was identified among the first patch-matrix neuronal markers (Herkenham and Pert, 1981).**

In this review, we focused on the implication of striatal dopamine, GABA and opioid **transmission** on food intake, with a specific focus on diet rich in fat. We discussed the potential

changes in these systems due to the palatable high-fat food consumption, and the influence of these systems on various aspects of feeding.

1 Implication of striatal dopamine (Table 1)

1.1 Dopamine and feeding

Dopamine is the most prominent and studied neurotransmitter in the striatal complex. It is synthesized from the essential amino acid tyrosine, by midbrain neurons of the ventral tegmental area and substantia nigra pars compacta expressing the enzyme tyrosine hydroxylase. These dopaminergic neurons project to different sections of the striatum, including the nucleus accumbens, where dopamine acts on projecting neurons which are inhibitory medium spiny neurons (MSNs) preferentially expressing either the D₁ receptor (D1-MSNs) or the D₂ receptor (D2-MSNs) (Gangarossa et al., 2013a; Gangarossa et al., 2013b; Oude Ophuis et al., 2014), **as well as on cholinergic** (Augustin et al., 2018; Cachope et al., 2012; Goldberg and Wilson, 2016; Lewis et al., 2020) **and on GABAergic interneurons** (Kubota et al., 1987; Tepper and Koós, 2016; Tepper et al., 2018; Tepper et al., 2010). **Dopamine release is controlled both at cell body and terminal levels. The fine control of dopamine neuron activity** (Marinelli and McCutcheon, 2014; Paladini and Roeper, 2014) **depends upon various neurotransmitters and modulators, including a balance between glutamatergic inputs from different brain regions and GABA inputs, in particular GABA neurons expressing the mu opioid receptors** (Bourdy and Barrot, 2012; Jalabert et al., 2011). **The recruitment of the dopamine system thus depends on neuroanatomical cascades implying various neurotransmitter pathways** (Blum et al., 2020; Gold et al., 2020). **An important control is also exerted through local dopamine terminal regulation** (Nolan et al., 2020), **through homosynaptic mechanisms, heterosynaptic signaling and diffusible messengers including metabolic factors. Notably, at circuitry level, the reciprocal influence between the striatal complex and the mesencephalic dopaminergic neurons is not a strict feed-back loop but it rather forms a neuroanatomical “spiral” or feed-forward loop within these actors** (Haber, 2014; Haber et al., 2000). **Such organization suggests that a localized manipulation of striatal neurotransmission may also indirectly impact other regions of the striatal complex.**

Fifty years ago, studies suggested that dopamine could be implicated in the control of feeding. Indeed, experimental alteration of central dopaminergic transmission was shown to impair food intake (Heffner et al., 1977; Ungerstedt, 1971). Using radioenzymatic assay on *post-mortem* dissected brain samples, it was then observed that feeding following food deprivation increased the production of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in given brain regions (Heffner et al., 1980). This increased dopamine turnover was present in the nucleus accumbens, the posterior hypothalamus and the amygdala, but not in other dopaminergic terminal fields such as the dorsal striatum. Beyond pointing to a link between feeding and dopamine, this study also highlighted the anatomical selectivity of this relation, suggesting the activation of functionally distinct subgroups of dopamine neurons with food intake (Heffner et al., 1980). With technical progress and the use of *in vivo* microdialysis or voltammetry, an increase in extracellular dopamine concentrations with food intake was reported in the striatum and the nucleus accumbens (Bassareo and Di Chiara, 1997; Di Chiara et al., 2004; Ferreira et al., 2012; Han et al., 2016; Hernandez and Hoebel, 1988; Joseph and Hodges, 1990; Joseph et al., 1989; McCullough and Salamone, 1992; Nakazato, 2005; Richardson and Gratton, 2008; Yoshida et al., 1992) (**Figure 2**). Moreover, confirming an anatomical specificity, several animal studies showed that palatable food preferentially increased those levels in the nucleus accumbens (Adachi et al., 2013; Fritz et al., 2018; Liang et al., 2006; Rada et al., 2012; Rada et al., 2010; Vollbrecht et al., 2016).

Beside normal feeding process, altered dopamine signaling has also been related to overeating and obesity (Bello and Hajnal, 2010; Rada et al., 2010; Wang et al., 2001). Interestingly, ingestion or injection of a high-fat solution was shown to preferentially increase extracellular dopamine levels in the medial part of the nucleus accumbens shell (Adachi et al., 2013; Di Chiara, 2005; Rada et al., 2012; Rada et al., 2010), whereas reduced basal dopamine levels as well as reduced dopaminergic response to fat intake has been observed in the nucleus accumbens of obesity prone rats (Rada et al., 2010). **At peripheral level, a high-fat diet was shown to decrease levels of *N*-acylethanolamines**, a family of appetite-regulating fatty acid amides, **in the jejunum of male Sprague-Dawley rats** (Diep et al., 2011). **Such change** in these fatty acid amides **has been related to changes** in dopamine levels in the dorsal striatum as the administration, *via* intraperitoneal catheters, of oleoylethanolamine (**OEA**),

one of the gastrointestinal lipid messenger whose synthesis is suppressed after prolonged exposure to a **high-fat** diet, was sufficient **to reverse** the dopamine deficiency (Tellez et al., 2013) (**Figure 3**). Interestingly, bariatric surgery, an effective long-term treatment of obesity, has also been found to impact OEA levels and modulate the dopaminergic system. Roux-en-Y gastric bypass (RYGB) surgery in diet-induced obese Sprague-Dawley rats decreased their appetite for fat while increasing intestinal OEA (Hankir et al., 2017), endogenous agonist of the peroxisome proliferator-associated receptor- α (PPAR- α). The action of OEA on this receptor led to vagally-mediated enhancement of feeding-induced dopamine release in the dorsal striatum, and interfering with one of these actors (OEA, vagus nerve, striatal D₁ receptor signaling) prevented RYGB beneficial effects on fat intake (Hankir et al., 2017).

Beyond the recruitment of dopamine itself, feeding and palatable food intake or regimen can also impact on other actors of the dopaminergic system, such as the dopamine receptors and transporter in the striatum, the nucleus accumbens and the ventral tegmental area (Bello et al., 2003; Davis et al., 2009; Huang et al., 2006; Jones et al., 2017; Narayanaswami et al., 2013; Patterson et al., 1998; South and Huang, 2008; Vucetic et al., 2010).

1.2 Change in dopamine receptors and transporter with feeding and fat

1.2.1 D₂ receptors

Using different imaging techniques, a relation between D₂ receptors and obesity has been proposed in humans. Indeed, positron emission tomography (PET)-scan and single-photon emission computed tomography (SPECT) showed a decrease in the availability of striatal D₂ receptors in obese male and female individuals compared to non-obese controls (de Weijer et al., 2011; Volkow et al., 2008). More specifically, the availability of striatal D₂ receptors was shown to be inversely proportional to the body mass index of the subjects (de Weijer et al., 2011; Volkow et al., 2008; Wang et al., 2001). **At** genetic level, individuals with at least one A1 allele of the **Taq1A** restriction fragment length polymorphism **are more** likely to become obese (Blum et al., 1996; Noble et al., 1994) (**Figure 4**). Dual-energy X-ray absorptiometry further showed that children with two A1 “risk” alleles have **higher energy intake, sugar consumption, body fat and abdominal adiposity** (Cardel et al., 2019) **than**

children with one or no risk alleles. This A1 allele of the Taq1A polymorphism (rs1800497) is located downstream of the *DRD2* gene, in an exon of the *ANKKI* gene, and its presence leads to reduced D₂ receptor binding in the striatum, mainly in the ventral caudate and putamen (Thompson et al., 1997). This A1 risk allele, and also another polymorphism (rs1799732) of the *DRD2* gene itself, showed an association with increased body mass index and/or obesity in pediatric population (Feistauer et al., 2018; Pinto et al., 2021), young population (Winkler et al., 2012), women (Aliasghari et al., 2021) and in adults (Beyer et al., 2021; Rivera-Iniguez et al., 2019).

While most studies converge to associate obesity with a decrease in D₂ receptors, it should be noted that some PET-scan studies reported no change (Eisenstein et al., 2013) or even an increase in D_{2/3} receptors availability in the striatal complex (caudate, putamen and nucleus accumbens) of obese individuals (Gaiser et al., 2016; Guo et al., 2014). These imaging studies mostly assessed the binding potential, which depends on the considered receptor availability and on the radiotracer binding affinity (van Galen et al., 2018). Apparent inconsistencies concerning D_{2/3} receptor data in obese population should thus be considered in light of the radiotracer that has been used. Indeed, when D_{2/3} receptors were studied using [¹¹C] raclopride or [¹²³I] IBZM there were reports of decreased D₂ receptor binding potential (de Weijer et al., 2011; van de Giessen et al., 2013; Volkow et al., 2008; Wang et al., 2001); while D₂-like receptor binding potential was increased when using [¹¹C](+)PHNO, which also acts as dopamine agonist that preferentially binds to D₃ receptor, or using [¹⁸F] fallypride (Gaiser et al., 2016; Guo et al., 2014; van Galen et al., 2018). The population criteria can be another important confounder (van Galen et al., 2018). Indeed, studies reporting an increase in D₂ receptor binding potential relied on body mass index ~35 kg/m² for the obese group (Gaiser et al., 2016), while decreased D₂ receptor binding potential was reported for obese individual with body mass index over 40kg/m² (de Weijer et al., 2011; van de Giessen et al., 2013; Wang et al., 2001). These aspects were discussed in details in a previous review article (van Galen et al., 2018). Using functional magnetic resonance imaging (fMRI) to understand the link between body mass index and striatal activation in response to food intake, obese individuals were shown to display a blunted dorsal striatum activation to palatable milkshakes compared to lean individuals, and this effect was amplified in those with the A1 allele (Stice et al., 2008). These results are consistent with the hypothesis that the dorsal striatum

is less responsive to food reward in obese individuals, seemingly due to decreased dopamine D₂ receptors availability and blunted dopamine signaling which may partly have a genetic origin. In diabetic patients, the *DRD2/ANKK1* Taq1A polymorphisms also interact with dietary factors to influence triglycerides levels (Ramos-Lopez et al., 2019); and, in individuals with the A1 risk allele, circulating postprandial triglycerides favored the response (BOLD signal in fMRI) of the ventromedial prefrontal cortex to food-related cues (Berland et al., 2020), suggesting that circulating triglycerides may be associated to this brain region response to food cue in a *DRD2*-dependent manner.

Interestingly, young individuals at high risk of obesity showed a greater activation of the dorsal striatum in response to food intake, which could suggest that, for some individuals, the initial vulnerability leading to obesity may correspond to an increased sensitivity of the dorsal striatum to food reward (Stice et al., 2011) that may later on evolve toward blunted responses when obesity develops. In individuals with such changes and blunted reward signaling, overeating might then reflect the need to reactivate a hypofunctional reward circuit in order to alleviate a negative emotional state (Moore et al., 2017), which is a situation that has also been proposed to accompany the development of addiction in some individuals (Koob, 2009; Koob and Le Moal, 2008) and can be associated with genetic risks (Blum et al., 2020). Importantly, response to specific food-related cues may remain high, thus resulting in a persistence of incentive salience sensitization (Robinson and Berridge, 1993) despite the compromised reward system. However, as in drug abuse, not all individuals may develop overeating for the same reason and through the same mechanism (Moore et al., 2017), which is important to consider to avoid oversimplification.

Mechanistic insights into the role of dopamine receptors in feeding behavior and obesity have however been mostly provided by animal studies in rodents. In concordance with human studies, the obese male Zucker rats have decreased striatal D₂ receptor levels compared with age-controlled lean rats (Hamdi et al., 1992). Interestingly, weight gain is inversely related to the striatal D₂ levels in both chow-fed and palatable high fat-fed rats (Johnson and Kenny, 2010), showing a similar correlation as in humans (de Weijer et al., 2011; Stice et al., 2010; Wang et al., 2001). Such relation has also been observed in mice, with chronic high fat diet-induced obese mice displaying a lower D₂ receptor

density in the rostral part of the caudate putamen compared to obese resistant and low fat fed mice (Huang et al., 2006).

It should be noted that D₂ receptors in the striatal complex are not only expressed by local neurons but are also present presynaptically as autoreceptors on dopamine terminals (Ford, 2014). Differentiating their respective role is not easy. Binge-eating on a high-fat diet in mice has however been shown to reduce dopamine uptake and increase D₂-mediated autoreceptor function in the nucleus accumbens (Jones and Fordahl, 2021).

While data converge in rodents and humans to suggest that a decrease in striatal D₂ receptors may be associated with obesity risk, it should be mentioned that contradicting results have on the other hand been reported concerning changes in D₂ receptor levels in the nucleus accumbens of mice and rats after a high fat diet consumption (Figure 4). Indeed, while some studies highlighted a decrease in striatal D₂ receptor levels in obese rats (Johnson and Kenny, 2010) specifically in the ventral and not the dorsal part of the striatum (Adams et al., 2015), other studies reported that a high fat diet increased D₂ receptor density in the nucleus accumbens and dorsal striatum in mice (Sharma and Fulton, 2013; South and Huang, 2008). More specifically, the increase in D₂ receptor density was observed using quantitative radiography in the shell of the nucleus accumbens, as well as in the ventral and dorsal part of the caudal caudate putamen of mice fed with a high fat diet for 20 days (South and Huang, 2008). These data completed an *in situ* hybridization study showing higher level of D₂ receptor mRNA expression in the core of the nucleus accumbens and in the ventral part of the caudate putamen in chronic high fat diet-induced obese mice compared to obese resistant and low fat fed mice (Huang et al., 2005). Using qPCR analyses, another study, in rats, also reported an increase in D₂ receptor gene expression in the caudate putamen of obesity prone Sprague-Dawley rats (Alsio et al., 2010). Taken together, there is no consensus in the literature on how an obesogenic diets alters D₂ receptor levels. It could well be that the type of diet (monosaturated *versus* polyunsaturated fats), the length of exposure to the diet, or the method of measuring (protein *versus* mRNA) could explain these contradictory reports. More research with compared diets and measuring availability of the receptors for signaling would add to our understanding of D₂ receptor responses to high fat diets.

1.2.2 *D₁ receptors and dopamine transporter*

In mice that were fed with a liquid fat solution, the single cell recording of **nucleus accumbens shell MSNs**, identified as D₁ or D₂ receptor expressing neurons using an optogenetic approach, revealed a **link** between **D₁-MSN** activity and liquid fat intake (O'Connor et al., 2015). Indeed, **these D₁-MSNs** displayed a reduction in their activity during feeding and an increase in activity at the end of the feeding (O'Connor et al., 2015) **In addition, *ex vivo* electrophysiology recording revealed that the inhibitory transmission from nucleus accumbens shell D₁-MSNs to the lateral hypothalamus was depressed in high-fat diet-induced overeating mice** (Thoeni et al., 2020). Furthermore, a subset of **D₁-MSNs** in the medial part of the shell of nucleus accumbens showed a c-Fos activation that was directly proportional to the amount of palatable food consumed (Durst et al., 2019).

Using reverse transcriptase PCR (RT-PCR), obesity prone Sprague-Dawley rats with long-term access to a high-fat and high-sugar diet were found to display a downregulation of D₁ receptor mRNA in the nucleus accumbens compared to obesity resistant rats (Alsio et al., 2010). This D₁ receptor mRNA downregulation in the nucleus accumbens was still observed after an 18 day-withdrawal period following the 7 weeks of high-fat and high-sugar diet (Alsio et al., 2010), highlighting the stable and very long-term changes that such regimen may induce. Concordantly, high fat fed mice displayed a reduced D₁ receptor protein expression in the nucleus accumbens (Sharma and Fulton, 2013). In addition, the study of intrauterine protein-restriction as a model for adulthood hyperphagia in male Wistar rats **also evidenced** a reduction in D₁ receptor mRNA levels in the medial shell of the nucleus accumbens of hyperphagic rats (Durst et al., 2019). **These hyperphagic rats** (Durst et al., 2019) **displayed** an increased intake of a rewarding solution (sweetened condensed milk), and an impaired response to reward-evoked neuronal activation in the medial shell of the nucleus accumbens compared to control rats. **Interestingly, Roux-en-Y gastric bypass (RYGB) surgery in diet-induced obese Sprague-Dawley rats increased D₁ receptor density in the striatum and reduced fat appetite** (Hankir et al., 2017) **(Figure 3)**. However, as it was the case for D₂ receptors, contradicting results have also been reported concerning changes in D₁ **receptors** in the nucleus accumbens in rats. For example, male Wistar rats under a diet rich in saturated lipids (palm oil) **had increased** D₁ receptor

level in the nucleus accumbens compared to control rats and rats under a diet rich in monounsaturated lipids (olive oil) (Hryhorczuk et al., 2016). This suggests that the observed molecular modifications may also depend on the type of fat consumed, with monounsaturated lipids seemingly having a protective effect (Hryhorczuk et al., 2016).

Besides changes in dopamine receptors associated with consumption of palatable foods, changes in the dopamine transporter in the striatal complex have also been reported. The density of the dopamine transporter has for example been reported to be decreased in the dorsal and ventral parts of the **caudate putamen**, but not in the nucleus accumbens, after 20 days of high-fat consumption (South and Huang, 2008). Moreover, a diet rich in palm oil has been shown to increase D₁ receptor levels but to decrease the dopamine transporter levels in the nucleus accumbens of Wistar rats (Hryhorczuk et al., 2016). These changes in dopamine transporter might be adaptive ones, as the density of dopamine transporter was also reported to be lower in the nucleus accumbens, **rostral caudate putamen** and hypothalamic regions of obese resistant mice, compared to chronic high fat diet-induced obese mice and low fat fed mice (Huang et al., 2006).

1.3 Impact of dopamine system manipulation on feeding and fat intake

1.3.1 Dopaminergic lesions and dopamine deficiency

Diet-induced obesity results in alterations in the dopamine signaling within the striatal areas. On the other hand, manipulation of dopamine systems also affects feeding behavior. This has been observed thanks to lesion experiments, genetic animal models, viral manipulations, and pharmacological approaches using dopamine reuptake inhibitors and dopamine receptor agonists and antagonists. A dose-dependent increase in food and water intake has for example been observed after injection of dopamine in the nucleus accumbens and striatum (Pal and Thombre, 1993). A complete bilateral lesion of substantia nigra dopaminergic neurons, using 6-hydroxydopamine, caused adipsia and aphagia in male Sprague Dawley rats (Ungerstedt, 1971). Similarly, dopamine deficient mice which were created by inactivation of the tyrosine hydroxylase gene in dopamine neurons **are** hypoactive and aphagic (Palmiter, 2008). The partial bilateral 6-hydroxydopamine lesion of the substantia nigra led to decreased consumption of chow (Joshi et al., 2021a); however, in one third of

the animals with slightly larger lesions, an increased fat intake was also observed during free choice high-fat high-sugar (fcHFHS) consumption (Joshi et al., 2021a), suggesting that these dopaminergic neurons influenced not only global feeding but also feeding choice. While the 6-hydroxydopamine lesion of substantia nigra dopaminergic neurons favored aphagia and adipsia, no significant alteration in food and water intake was observed in female Sprague-Dawley rats after a radio-frequency lesion of the same structure (Hodge and Butcher, 1980), which beyond dopaminergic cells would also suppress GABAergic and glutamatergic neurons. At terminal level, a bilateral 6-hydroxydopamine lesion of the nucleus accumbens led to an increased rebound of food intake in 23-hour food deprived male Wistar rats (Koob et al., 1978); and **when the dopaminergic lesion specifically targets** the lateral nucleus accumbens (but **not the** medial nucleus accumbens), **it** led to preferential increase in fat intake **in** male Sprague-Dawley rats **fed** with free choice high-fat high-sugar diet (Joshi et al., 2021a).

To study the impact of dopamine deficiency and dopamine repletion on feeding behavior, a model of dopamine-deficient mice was created by inactivation of the tyrosine hydroxylase gene in dopamine neurons (Palmiter, 2008; Zhou and Palmiter, 1995). In addition to being hypoactive and aphagic, these mice died of starvation within 4 weeks, which could be reversed by a daily chronic administration of the precursor of dopamine L-DOPA (Palmiter, 2008). In these mice, feeding behavior sufficient for survival could also be restored if the dopamine system was locally rescued by a pharmacological or viral-approach (Hnasko et al., 2006; Palmiter, 2008; Sotak et al., 2005; Szczyпка et al., 2001; Zhou and Palmiter, 1995). Such rescue has for example been done by ectopically expressing tyrosine hydroxylase in the central or lateral caudate putamen using a recombinant adeno-associated virus (Szczyпка et al., 2001), or by re-expressing the enzyme in the nigrostriatal pathway by doing striatal injection of retrograde canine adenoviruses (Hnasko et al., 2006; Sotak et al., 2005). By restoring the dopaminergic levels in given regions, these studies highlighted the role of dopamine in the dorsal striatum in dopamine-related behaviors including feeding (Hnasko et al., 2006; Sotak et al., 2005). Interestingly, the data also suggested that there is a fundamental difference between feeding for sustenance and preferably choosing rewarding/palatable substances, with the latter also involving other brain regions such as the nucleus accumbens. Indeed, dopamine replacement in either the caudate putamen or the nucleus accumbens restored preference for sucrose in the dopamine-

deficient mice, while a rescue of the normal feeding behavior was only observed after localized dopamine production in the caudate putamen but not in the nucleus accumbens (Szczyepka et al., 2001).

1.3.2 Dopamine uptake inhibition

As mentioned previously (see Section 1.1), obesity and high fat intake might impact the feeding behavior via the regulation of striatal dopamine signaling. To better understand the role of the striatal complex in different aspects of feeding, some studies used monoamine reuptake inhibitors to increase extracellular dopamine levels. Diet-induced obese rats treated with tesofensine, a triple monoamine uptake inhibitor blocking dopamine, serotonin and norepinephrine transporters, displayed lower caloric intake and weight gain, with decreased $D_{2/3}$ receptor availability in the nucleus accumbens and the dorsal striatum (van de Giessen et al., 2012; van de Giessen et al., 2013). Bupropion, another catecholamine uptake inhibitor with a preferential action on the dopamine transporter, has been used for a long time as an antidepressant drug and also has an anorexic effect that depends on the activation of D_1 and D_2 receptors in the nucleus accumbens shell (Kalyanasundar et al., 2015). In an effort-related task where rats could choose between high carbohydrate pellets and freely available lab chow by pressing a lever, systemic bupropion increased the progressive ratio lever pressing and decreased the chow intake (Randall et al., 2014). This action of bupropion was accompanied by an increase in dopamine levels and in the phosphorylated form of the dopamine and cyclic-AMP related phosphoprotein 32 kDaltons (pDARPP-32) in the nucleus accumbens core (Randall et al., 2014). The effort provided to obtain palatable food involves an interaction between D_2 receptors and the adenosine A_{2A} receptors in the nucleus accumbens, as shown by the impact of antagonists delivered in the nucleus accumbens core on the lever pressing for high carbohydrate operant pellets *versus* regular chow intake in rats (Farrar et al., 2010).

1.3.3 Dopamine receptor manipulation

Among the various aspects of feeding, changes in dopamine transmission has also been associated with reward deficits and compulsive responding for food related to obesity. In rats, an extended access to a palatable high-fat diet induces obesity, with emergence of addictive-like

behaviors such as compulsive responding for food and reward (Johnson and Kenny, 2010). The lentivirus-mediated knockdown of dorsal striatal D₂ receptors accelerated the onset of this reward deficit and favored compulsive-like eating in animals with extended access to a palatable high-fat diet, but not to regular chow (Johnson and Kenny, 2010); even though an overall D₂ receptor knock down did not result in overconsumption of palatable food and did not induce obesity (Beeler et al., 2016; Friend et al., 2017). D₂ receptor signaling is considered important to regulate palatable and/or caloric food intake, and low levels of D₂ receptor have been proposed to predispose an individual towards obesity. It is noteworthy that this influence of D₂ receptors is not limited to palatable food intake, but it also extends to drugs of abuse and for example intake of alcohol (Martinez et al., 2012; Trifilieff and Martinez, 2014). The density or availability of D₂ receptors was indeed reduced in alcoholics (Heinz et al., 2004; Hietala et al., 1994; Martinez et al., 2005; Volkow et al., 1996) and, in rodents, overexpression of the D₂ receptor using an adenoviral vector delivered in the nucleus accumbens reduced alcohol consumption in genetically inbred alcohol-preferring and non-preferring rats (Thanos et al., 2004).

Dopaminergic influence on food intake was also explored using agonists and antagonists of the dopamine receptors. Surprisingly, the systemic administration of either dopamine receptor agonists or antagonists mostly produced a converging response, reducing the overall food intake in a dose-dependent manner (Baker et al., 2001; Gilbert and Cooper, 1985; Rolls et al., 1974; Terry and Katz, 1992; Zarrindast et al., 1991). Systemic dopamine antagonism also reduced water intake (Ungerstedt, 1971). However the action of those drugs on food intake may differ depending on the considered dose. For example, an intraperitoneal administration of the D₂ receptor antagonist raclopride favored food intake at intermediate doses, while at a higher dose it impaired feeding behavior by increasing the latency to feed and drink (Clifton et al., 1991). Similarly, the consumption of a high fat diet after subcutaneous administration of raclopride was increased at low doses, but decreased at a higher dose (Baker et al., 2001). Centrally, however, D₂ receptor antagonism in the core and medial shell of the nucleus accumbens increased the duration and decreased the numbers of feeding bouts even though it did not affect the overall intake of solid or liquid food (Baldo et al., 2002; Lardeux et al., 2015), and even though the same local dose of raclopride did reduce the

hyperlocomotion induced by an amphetamine injection (Chausmer and Ettenberg, 1999). Similarly, the injection of raclopride in the nucleus accumbens did not change fat intake after saline or DAMGO injection in the nucleus accumbens (Will et al., 2006), or when raclopride was delivered in the lateral shell of the nucleus accumbens (Joshi et al., 2021b). However, despite the lack of change in food intake, it has been shown that bilateral injection of raclopride in the nucleus accumbens (Bernal et al., 2008) or in the amygdala (Bernal et al., 2009; Malkusz et al., 2012) decreased the expression or maintenance of a preference for a flavor paired with a fructose/saccharin solution; while raclopride in the medial prefrontal cortex or in the medial orbital frontal cortex reciprocally blocked the learning/acquisition or the expression of this fructose-conditioned flavor preferences in rats (Malkusz et al., 2012; Malkusz et al., 2015). In addition, the infusion of raclopride in the nucleus accumbens prevented the change in meal frequency and duration associated with binge-eating of a sucrose solution in female rats (Suarez-Ortiz et al., 2018). Moreover, deep brain stimulation of the medial nucleus accumbens, but not of the dorsal striatum, reduced the binge eating of high fat in mice (Halpern et al., 2013), and an intraperitoneal raclopride administration 30 minutes before the deep brain stimulation blocked this inhibitory effect on high-fat binging (Halpern et al., 2013). Besides, infusion of raclopride in the nucleus accumbens not only blocked the feeding-induced decrease in nucleus accumbens glutamate in rats, but even locally increased these extracellular levels of glutamate during feeding (Mikhailova, 2002, 2003; Saul'skaia and Mikhailova, 2001; Saulskaya and Mikhailova, 2002).

The D₁ receptor knock-out mice were resistant to diet-induced obesity (Grippio et al., 2020). In rats, after systemic administration, the D₁ receptor antagonist SCH23390 had a small but significant effect on total food intake and feeding patterns, with a reduction of the feeding rate and number of pellets consumed 3 hours after the intraperitoneal injection (Clifton et al., 1991). It also decreased water consumption (Clifton et al., 1991; Gilbert and Cooper, 1987; Ljungberg, 1989). After central administration, SCH23390 had site-specific effects. It decreased water consumption after local delivery of the SCH23390 in the ventrolateral striatum (Inoue et al., 1995). It had however no effect on total food intake when injected in the nucleus accumbens (Baker et al., 2001; Inoue et al., 1995;

Will et al., 2006) or in the lateral hypothalamus (Yonemochi et al., 2019), while a dose dependent suppression in food intake was observed when SCH23390 was injected in the paraventricular hypothalamic nucleus (Mirmohammadsadeghi et al., 2018). In addition, SCH23390 did not alter the consumption of high fat after a saline or a DAMGO injection in the ventrolateral striatum (Will et al., 2006). Although SCH23390 did not change the overall consumption of different types of food, it decreased the expression or maintenance of a preference for a flavor paired with a fructose/saccharin solution when SCH23390 was injected in the nucleus accumbens or in the amygdala (Bernal et al., 2009; Bernal et al., 2008; Malkusz et al., 2012), and it blocked the acquisition of this preference when injected in the medial prefrontal or orbital frontal cortices in rats (Malkusz et al., 2012; Malkusz et al., 2015). Surprisingly, when SCH23390 was specifically infused in the lateral nucleus accumbens (and particularly in its rostral extent), it favored fat intake in rats on a free choice high-fat high-sugar diet (Joshi et al., 2021b), with no local effect of a D₂ receptor antagonist (raclopride), which highlights the complexity of dopamine-related food controls and suggests differences between the considered striatal sub-regions and related sub-circuits.

In rats, the systemic injection of the D₁ receptor full agonist SKF82958 (Terry and Katz, 1992), of the D₁ receptor partial agonist SKF38393, of the D₂ receptor agonist bromocriptine or of the D_{2/3} receptor agonist quinpirole decreased food intake in a dose-dependent manner (Zarrindast et al., 1991), and the D₂ receptor agonist bromocriptine also decreased food intake in genetically obese Zucker and diet-induced obese rats (Davis et al., 2009; Davis et al., 2006). With the partial agonist SKF38393, the precise impact of systemic injections may however depend on the dose. Indeed, its subcutaneous injection facilitated the intake of palatable food and, at a low dose, facilitated overall feeding (Cooper and Al-Naser, 2006; Cooper et al., 1992; Mirmohammadsadeghi et al., 2018), while at high dose it had an inhibitory action on feeding (Cooper and Al-Naser, 2006; Cooper et al., 1990; Gilbert and Cooper, 1985; Martin-Iverson and Dourish, 1988; Rusk and Cooper, 1989). Different actions of SKF38393 and of quinpirole on food preference and on food intake were also observed (Cooper and Al-Naser, 2006). While subcutaneous SKF38393 increased the consumption of palatable sweet chocolate biscuit, it decreased food pellet consumption; and while subcutaneous quinpirole decreased sweet chocolate biscuit consumption, it increased food pellet consumption (Cooper and Al-

Naser, 2006). These observations highlight the necessity to be cautious in interpreting and generalizing data related to feeding behavior. **Beside the drug selectivity, the dose aspect and the food nature and context, the considered neuroanatomical site is also critical. Indeed, central administration of SKF38393 in the nucleus accumbens had no effect on food intake (Phillips et al., 1995), while its administration in the VTA dose-dependently increased regular chow intake in 18h food-deprived Wistar rats (Saebi Rad et al., 2020), and its bilateral administration or the one of quinpirole in the lateral hypothalamus also increased food intake, which was blocked by respective injection of SCH23390 or sulpiride in the lateral hypothalamus (Yonemochi et al., 2019). Such finding with D₁ receptor stimulation in the lateral hypothalamus was further supported by the increase in food intake of Sprague-Dawley rat following injection of the full agonist SKF81297 in the perifornical lateral hypothalamus (Chen et al., 2014). Concerning the D₂ receptor agonist bromocriptine, its intracerebroventricular administration (Evans and Eikelboom, 1987) or its local infusion in the nucleus accumbens (Inoue et al., 1997) increased food intake and meal duration in normal rats, which may reflect compensatory intake following decreased reward signaling. Indeed, as stated above, D₂ receptors are also present presynaptically on dopamine terminals. In fact, systemic and even local injections of a D₂ receptor agonist thus leads to activation of both postsynaptic and presynaptic D₂ receptors (Ford, 2014; Hartesveldt et al., 1992; Horst et al., 2019), inhibiting respectively D₂-MSNs and dopamine release.**

Some regions of the striatal complex, such as the nucleus accumbens shell, are also enriched in D₃ receptors, a sub-type of D₂-like receptors. Their influence on feeding has been assessed using D₃ receptor deficient mice (D₃R^{-/-}). The injection of the non-metabolizable glucose analogue 2-deoxy-D-glucose, of mercaptoacetate inducing lipoprivation by blocking beta-oxidation of medium- to long-chain fatty acids, or of peripheral insulin, increased food intake in wild-type mice, but failed to do so in male D₃R^{-/-} mice (Benoit et al., 2003). This work was completed by showing some sex-related differences: D₃R^{-/-} female mice increased their body fat (but not their body weight) under either high fat or normal standard chow, while D₃R^{-/-} male mice increased both body weight and body fat when provided access to a high fat diet (McQuade et al., 2004).

1.3.4 MSN manipulation

Striatal MSN neurons, expressing one or the other of dopamine receptors, have also been manipulated to study their role in food intake. The optogenetic inhibition of D1-MSNs, but not of D2-MSNs, increased food intake and prolonged consumption in *ad libitum* fed mice (O'Connor et al., 2015). In addition, the chemogenetic activation of D1-MSN in the nucleus accumbens (Luo et al., 2018) and the optogenetic activation of D1-MSNs terminals in the lateral hypothalamus suppressed feeding, even when mice were food-deprived for 24 hours (Luo et al., 2018; O'Connor et al., 2015). A population of GABAergic neurons in the lateral hypothalamus was found to be the functional target of D1-MSNs and their direct inhibition stopped feeding even in food-deprived mice (O'Connor et al., 2015).

Recently, it has been shown that dietary triglycerides can be metabolized within the mesocorticolimbic system itself, and can modulate dopamine-associated behaviors by gating the activity of D2-MSNs through a mechanism that involves the action of the lipoprotein lipase (Berland et al., 2020; Berland et al., 2021). *Ex vivo* recording of striatal and accumbens D1-MSNs and D2-MSNs further demonstrated that only D2-MSNs were hyperpolarized by an exposure to the triglyceride triolein, an effect that was lost in mice lacking the lipoprotein lipase *Lpl* gene in D2-MSNs (Berland et al., 2020).

1.3.5 Developmental manipulation

Recent experimental data support the idea of early links between dopamine system and feeding with consequences at adulthood. This developmental aspect of dopamine/feeding interactions is critical as specific events, diets or system manipulation at prenatal, perinatal or periadolescent stage could impact adult feeding behavior and risk of obesity.

For example, mice genetically modified to overexpress D₂ receptors in striatal MSNs during development showed an accelerated obesity when they were fed with a high fat diet in adulthood (Labouesse et al., 2018). This observation was proposed to result from a reduction in brown adipose tissue thermogenesis leading to reduced energy expenditure, rather than from an increase in eating (Labouesse et al., 2018), and led to propose that an alteration in the striatal dopamine system during

development could be a major predisposition factor leading to obesity in adulthood. Reciprocally, a deficit of n-3 polyunsaturated fatty acids from gestation to adulthood in mice led to motivational deficits at adulthood, associated with an increased collateral inhibition of D2-MSNs onto D1-MSNs in the nucleus accumbens, resulting in a decreased excitability of D1-MSNs (Ducrocq et al., 2020). This MSN alteration can be prevented by genetically restoring n-3 polyunsaturated fatty acids levels selectively in dopamine D2-MSNs (Ducrocq et al., 2020). Interestingly, food supplementation in n-3 polyunsaturated fatty acids starting at birth reversed the motivational deficits in adulthood, while it failed to do so when supplementation started at weaning (Ducrocq et al., 2020). These data highlighted a critical developmental period during which n-3 polyunsaturated fatty acids may interact with dopamine system development. High-fat diet during this perinatal period in rodents can also durably impact the dopaminergic system. Offspring from mothers fed with a high-fat diet during the last week of pregnancy and the whole lactation period showed altered mesocorticolimbic dopamine neurotransmission, without however notable change in levels of D₁ and D₂ receptors or dopamine transporter in the dorsal striatum and in the core and shell of the nucleus accumbens (Naef et al., 2008). The genomic analysis of midbrain dopamine centers (ventral tegmental area and substantia nigra pars compacta) in male and female offspring of mice fed with a high-fat diet during lactation revealed an altered expression of genes related to neuronal development, ion channel expression, and locomotor behavior (Lippert et al., 2020). These changes resulted in an attenuated activity of dopamine midbrain neurons, a reduction of the connectivity to their downstream targets, and a decrease in a stimulus-evoked dopamine release in the striatum as well as an alteration of dopamine-related behaviors (Lippert et al., 2020). In particular, it increased the intake of palatable food and sucrose in female, but not in male, offspring thus showing that developmental consequences of specific diet exposure may also be sex-dependent (Lippert et al., 2020).

Adolescence may also be a critical developmental period when an obesogenic diet can make the dopaminergic system vulnerable to later reward-related disorders. As example, chronic consumption of a high-fat diet during the periadolescent period in the rat enhanced the sensitization to amphetamine in adults, leading to molecular plasticity and increased sensitization of extracellular dopamine levels in the nucleus accumbens and of behavioral response (Naneix et al., 2017).

1.4 Conclusion on striatal dopamine in feeding behavior

Overall, the relation between dopamine signaling and feeding is complex. Dopamine and its receptors are important for the control of feeding and could contribute to different aspects of food motivation and reward. Moreover, dopamine signaling may mediate the palatability of food, particularly when rich in fats. Besides, increased high fat palatable diet consumption also alters the release of dopamine, the expression of dopamine receptors and of the dopamine transporter, which could further promote weight gain, obesity and related co-morbidities.

2 GABA (Table 2)

2.1 GABA receptors in the nucleus accumbens

Gama-aminobutyric acid (GABA) is the principle inhibitory neurotransmitter in the brain. The striatal complex is primarily composed of GABAergic neurons, some of them being interneurons but most of them being **MSNs** providing long range projections outside the striatum to the ventral pallidum, globus pallidus, hypothalamic structures and midbrain structures (Oorschot, 2016). Besides being an inhibitory structure, the striatal complex also receives inhibitory inputs **from local interneurons, from local axon collaterals from MSNs themselves** (Gerfen and Bolam, 2016), **and from inputs from other brain regions, such as** the cortex (Melzer et al., 2017; Rock et al., 2016) or the ventral pallidum (Vachez et al., 2021) among others.

GABA receptors within the nucleus accumbens play a role in feeding behavior. **Ionotropic GABA_A receptors and metabotropic GABA_B receptors are both distributed throughout the striatum (caudate putamen and nucleus accumbens)** (Fujiyama et al., 2002; Goetz et al., 2007; Ikeda et al., 2012; Lacey et al., 2005; Matsumoto, 1989; Saigusa et al., 2021; Schwarzer et al., 2001). **GABA_A receptors are mostly postsynaptic (Tretter and Moss, 2008), while GABA_B receptors are expressed both at presynaptic and postsynaptic level in the striatal complex** (Lacey et al., 2005; Smith et al., 2000). **The GABA_B receptors presynaptically present on corticostriatal excitatory terminals can limit the vesicular release of glutamate from MSN afferents** (Calabresi et al., 1990; Kupferschmidt and

Lovinger, 2015; Logie et al., 2013; Margeta-Mitrovic et al., 1999), and thus decrease the excitatory synaptic strength (Manz et al., 2019).

The GABA_A receptor agonist muscimol delivered in the nucleus accumbens increased the operant responding for food (Stratford and Wirtshafter, 2012). More generally, muscimol or baclofen, a GABA_B receptor agonist, increased food intake in a dose-dependent manner when they were locally injected in the medial nucleus accumbens shell (Basso and Kelley, 1999; Pulman et al., 2010; Soderpalm and Berridge, 2000; Stratford and Kelley, 1997; Ward et al., 2000). This action may preferentially concern nutrient-relevant food intake as an infusion of muscimol (20 ng/0.5 μ L and 50 ng/ 0.5 μ L) in the medial shell of the nucleus accumbens increased the intake of chow, fat and sugar in separate cohorts of experiments, without affecting water, saline and saccharine solution intake (Basso and Kelley, 1999; Lopes et al., 2007). Moreover, when both food rich in carbs and food rich in fat were presented simultaneously, muscimol delivered in this subregion of the nucleus accumbens increased the consumption of those two types of food to the same degree, without inducing a preference for one or the other (Basso and Kelley, 1999). This effect of local muscimol on food intake was preferentially observed in the medial shell of the nucleus accumbens, as it was not present with injections in the lateral or ventral nucleus accumbens (Basso and Kelley, 1999), and it has been in particular highlighted for injections in the rostral part of the medial nucleus accumbens (Lopes et al., 2007). Interaction between diet components also influenced the impact of local muscimol injection. For example, while muscimol injected in the nucleus accumbens at a high dose (100 ng) produced a large increase in the intake of a sucrose solution, it induced a decrease in 10% ethanol consumption but a significant increase in the intake of an ethanol-sucrose mixture (Stratford and Wirtshafter, 2011). Furthermore, the muscimol-induced feeding was sensitized by exposure to sweetened fat (Newman et al., 2013).

Research also addressed the circuitry and/or neurochemical actors mediating this effect of muscimol on feeding. An opioid component is for example likely present, as nucleus accumbens muscimol-mediated food intake was decreased after pretreatment with an opioid receptor antagonist delivered in the nucleus accumbens (Khaimova et al., 2004), but not with dopamine receptor

antagonists (Richard et al., 2013). In fact, intraaccumbal muscimol even further increased food intake induced by the intraperitoneal injection of the D₂ receptor antagonist haloperidol (Meena et al., 2009). At neuroanatomical level, muscimol in the nucleus accumbens increased Fos-like immunoreactivity in the lateral hypothalamus, and infusion of the NMDA receptor antagonist D(-)-AP5 in the lateral hypothalamus concomitantly suppressed the feeding induced by the nucleus accumbens shell muscimol injection in a dose-dependent manner (Stratford and Kelley, 1999). The large increase in food intake induced by muscimol delivery in the nucleus accumbens shell was also potently suppressed by blocking central Y1 or Y5 receptors, suggesting that food intake mediated by the nucleus accumbens shell was dependent on the release of neuropeptide Y (Stratford and Wirtshafter, 2004). The hyperphagia induced by muscimol infusion in the nucleus accumbens was not altered by co-infusion of muscimol in the basolateral amygdala, whereas co-infusion of either muscimol or tetrodotoxin in the central nucleus of amygdala reduced feeding in a dose-dependent fashion (Baldo et al., 2005). Together, these findings suggest that feeding elicited by the nucleus accumbens GABA_A receptors requires the lateral hypothalamus and the central nucleus of the amygdala.

In addition to GABA_A receptor stimulation, some studies have been carried out using GABA_B receptor agonists. Many studies concerned global manipulation of these receptors, with systemic injection. Thus, a systemic injection of the GABA_B receptor agonist baclofen reduced the consumption of palatable food (Avena et al., 2014; Buda-Levin et al., 2005; Rao et al., 2008), but this action was dependent on the dose injected, on the type of diet considered and on food accessibility, and on interactions with other systems such as the opioid system. **Centrally, GABA_B receptor signaling in D1-MSNs from the caudate putamen has been shown to suppress binge eating under a high fat diet in mice (Sun et al., 2021).** In contrast, the local administration of baclofen in the medial nucleus accumbens stimulated the intake of solid food, without affecting the intake of a palatable sweet glucose/saccharine solution (Khaimova et al., 2004; Lopes et al., 2007; Ward et al., 2000). The increased food intake after baclofen injection in the nucleus accumbens was suppressed with local pretreatment with delta and kappa opioid receptor antagonists (Khaimova et al., 2004).

Different to findings with GABA agonists, the nucleus accumbens injection of the GABA_A receptor antagonist bicuculline and of the GABA_B antagonist saclofen had no effect *per se* on food

intake (Znamensky et al., 2001). However, these antagonists had opposite and dose-dependent effects on the feeding response elicited by the mu-selective opioid agonist DAMGO (Znamensky et al., 2001). Food intake induced by DAMGO injection in the nucleus accumbens was increased by pretreatment with bicuculline in nucleus accumbens, while intra-accumbens pretreatment with saclofen decreased it (Znamensky et al., 2001). While local bicuculline favored DAMGO-induced feeding (Znamensky et al., 2001), it suppressed food intake induced by intraperitoneal haloperidol (Meena et al., 2009). Pretreatment with saclofen in either the ventral tegmental area or the medial shell of nucleus accumbens also blocked the feeding induced by the GABA_B receptor agonist baclofen delivered in the nucleus accumbens or ventral tegmental area respectively (Miner et al., 2010). Moreover, rats kept on a diet with separated sources of protein, carbohydrate and fat consumed preferentially about 97% of their calories from fat after bicuculline infusion in the ventral pallidum (Covelo et al., 2014).

2.2 *GABA receptors in the ventral pallidum*

The ventral pallidum is a major output of the nucleus accumbens, and the nucleus accumbens neurons projecting to the ventral pallidum neurons can co-express GABA and the neuropeptide enkephalin, a delta and mu-opioid receptor ligand (Kupchik et al., 2014). Upon GABA_A receptor blockade in the ventral pallidum using bicuculline, an increase in food intake in satiated rats was observed, which suggested the involvement of the nucleus accumbens shell - ventral pallidum - lateral hypothalamus pathway in the control of feeding behavior (Covelo et al., 2014; Stratford et al., 1999). It has thus been proposed that stimulation of GABA_A receptors in the ventral pallidum would result in behavioral effects similar to those produced by inhibiting the nucleus accumbens dopamine transmission (Covelo et al., 2014; Farrar et al., 2008). Injection of muscimol (5.0-10.0 ng) into the ventral pallidum decreased lever pressing for palatable sucrose pellets while favoring the direct consumption of regular chow in rats under a food choice task requiring a fixed ratio of 5 lever press to obtain the sucrose pellets (Farrar et al., 2008). This observation was thus supportive of an influence on the motivation or reward value of the food, rather than on basic feeding behavior itself. Such conclusion was further supported by the fact that reward-specific firing was observed in a greater

proportion of neurons in the ventral pallidum than in the nucleus accumbens following sucrose or maltodextrin delivery (Ottenheimer et al., 2018). Surprisingly, the onset and peak of the reward-specific information occurred earlier in the ventral pallidum (Ottenheimer et al., 2018), suggesting that information was provided to this structure from another source than the nucleus accumbens. In addition, for the respective trials with the two palatable carbohydrates, sucrose and maltodextrin solution which have equivalent caloric value but distinct tastes, a larger pallidal response was observed with the sucrose solution compared to the maltodextrin one. However, when sucrose was replaced with water, the pallidal response for the maltodextrin solution increased (Ottenheimer et al., 2018). Besides being an output structure of the nucleus accumbens, the ventral pallidum also projects to the nucleus accumbens. Indeed, it has been recently shown that ventral arypallidal neurons of the ventral pallidum project dense web-like processes throughout the nucleus accumbens shell, forming inhibitory *synapses* (Vachez et al., 2021). The optogenetic activation of these ventral arypallidal neurons promoted the consumption of a sucrose solution and their inhibition attenuated it (Vachez et al., 2021). Moreover, a fiber photometry study suggested that ventral arypallidal neurons may mediate food palatability, as indicated by the increased calcium signal during consumption of rewarding sucrose solution over water consumption, and decreased calcium signal during bitter (unpleasant) quinine consumption (Vachez et al., 2021).

2.3 Conclusion

Taken together, data suggest that stimulation of either GABA_A or GABA_B receptors within the nucleus accumbens promotes feeding in general, and may not be specific to palatable feeding. The medial shell of the nucleus accumbens seemed to be the region the most sensitive to GABA effects on feeding behavior. On the other hand, GABA antagonism did not exert a major effect on feeding by itself, however it could reduce intake when feeding was stimulated by opioids. Within the ventral pallidum, GABA also plays an important role with effects on feeding that are in part opposite to effects of GABA in the nucleus accumbens, and with an influence of pallidal GABA transmission on palatable feeding.

3 Opioids (Table 3)

3.1 Opioid and feeding

Feeding increases the release of endogenous opioid peptides, which could be influenced by pathological state or by food palatability. For example, higher plasmatic β -endorphin levels were reported in obese persons (Facchinetti et al., 1986; Scavo et al., 1990). In rats, centrally, opiate binding and radioimmunoassays evidenced an hypothalamic recruitment of β -endorphin, but not dynorphin, with the consumption of a palatable food (Dum et al., 1983). The use of *in vivo* microdialysis also showed that extracellular levels of endogenous enkephalins (both met-enkephalin and leu-enkephalin), but not of dynorphin, increased in the rat dorsal striatum after consumption of a palatable food (DiFeliceantonio et al., 2012). Furthermore, evidence of central endogenous opioid peptide recruitment was obtained in humans thanks to PET-scan using the mu opioid-selective ligand [^{11}C] carfentanil (Tuulari et al., 2017). Surprisingly however, such central opioid release with meals was observed throughout human brain regions, including the ventral striatum, dorsal caudate and putamen, insular cortex, amygdala, thalamus, etc. and was not associated with hedonic aspects of feeding in a situation where palatable and nonpalatable meals were matched in terms of energy content and nutrients (Tuulari et al., 2017). In minipigs, [^{11}C] carfentanil PET-scan evidenced acute opioid release in the nucleus accumbens and cingulate cortex with sucrose intake, and a down-regulation of receptor densities after 12 days of such sucrose regimen (Winterdahl et al., 2019). PET scan with [^{11}C] carfentanil also highlighted a decreased availability of mu opioid receptors in the ventral striatum of morbidly obese women (Karlsson et al., 2015), men (Burghardt et al., 2015) and obesity risk prone young males (Kantonen et al., 2021), which could reflect either decreased receptor expression or higher basal release of opioid peptides. This decrease in mu opioid receptor availability in obese persons compared to healthy weight controls (Karlsson et al., 2015) was reversed when people underwent bariatric surgery for weight loss treatment (Karlsson et al., 2016). This emphasizes that opioids also play an important role in human obesity.

The opioid system is also important for the brain response to cues related to palatable food. Indeed, lower baseline in mu opioid receptor availability in the human thalamus was associated with

stronger BOLD-fMRI response in the orbitofrontal and cingulate cortices, thalamus and ventral striatum when viewing appetizing *versus* bland foods (Nummenmaa et al., 2018). Low mu opioid receptor availability might thus contribute to risk factors by favoring anticipatory reward response.

In the early 1980s, the role of systemic manipulation of the opioid system on the modulation of ingestive behavior was tested. In the rat, opioid receptor agonists and antagonists have an opposite effect on such behavior (Jalowiec et al., 1981), with morphine injected peripherally or centrally increasing food intake (Calignano et al., 1993; Jalowiec et al., 1981; Majeed et al., 1986; Mucha and Iversen, 1986; Verty et al., 2003). Also for humans, early reports showed that opiates increased food intake (Martin et al., 1963), and that blocking opioid receptors decreased food intake in humans mostly by reducing food pleasantness (Yeomans and Wright, 1991; Yeomans et al., 1990).

To understand the anatomical basis of opioid effect, local injections were then performed in the striatal complex. The three types of opioid receptors, mu opioid receptors, delta opioid receptors and kappa opioid receptors, are indeed locally present, both presynaptically on some afferents and post-synaptically in both D1-MSNs and D2-MSNs (Derouiche and Massotte, 2019; Escobar et al., 2020; Laurent et al., 2014; Pellissier et al., 2018; Tejada et al., 2017). Mu opioid receptors are greatly enriched in the patch compartment (Herkenham and Pert, 1981); and while delta opioid receptors are also more present in the patch compartment and exo-patch neurons (a set of neurons residing in matrix zones but having neurochemistry, connectivity and electrophysiological characteristics resembling patch neurons) (Chu Sin Chung et al., 2015; Miura et al., 2007; Pellissier et al., 2018; Prager and Plotkin, 2019; Smith et al., 2016), their presence is more scattered throughout the striatum with an expression in cholinergic interneurons (Pellissier et al., 2018). Kappa opioid receptors are present in both the patch and the matrix (Prager and Plotkin, 2019); and if neurons of both MSNs types may express these receptors, their presence is higher in D1-MSNs (Escobar et al., 2020; Tejada et al., 2017). Being also present on the terminals of some dopaminergic afferents, the activation of kappa opioid receptors decreases dopamine release in the nucleus accumbens (Di Chiara and Imperato, 1988; Escobar et al., 2020; Spanagel et al., 1992) and the dorsal striatum (Gehrke et al., 2008).

A microinfusion of mu opioid receptor agonists such as [D-Ala²,N-Me-Phe⁴,Gly-ol⁵]-enkephalin (DAMGO) in the nucleus accumbens and striatum robustly increased food intake in a dose-dependent manner, and this action was blocked by co-administration of the opioid antagonist naltrexone (Bakshi and Kelley, 1993). In operant procedures, DAMGO injection in the nucleus accumbens also increased lever pressing for food (Cunningham and Kelley, 1992; Stratford and Wirtshafter, 2012). Reciprocally, sucrose licking *per se* was in fact inhibited by mu opioid receptor antagonists in the nucleus accumbens (Katsuura and Taha, 2014), and the increase in sucrose palatability induced by food deprivation was also blocked by an infusion of naloxone in the nucleus accumbens or the ventral pallidum (Wassum et al., 2009). Moreover, both mu and kappa receptor antagonists in the nucleus accumbens reduced food intake under food deprivation and glucoprivic conditions, while only the mu receptor antagonist reduced palatable food intake (10% sucrose) (Bodnar et al., 1995; Kelley et al., 1996; Ward et al., 2006). It suggested that the link between the opioid system and feeding may also depend on the type of food consumed. It was for example shown that a DAMGO infusion in the rat nucleus accumbens increased the intake of fat or carbohydrate when these diets were provided separately, but when the rats were provided with choice between fat and carbohydrate, they preferentially ingested fat only (Zhang et al., 1998) and this influence of DAMGO was dose-dependent (Zhang and Kelley, 2000). This influence may be independent from the caloric aspect of fat. Indeed, DAMGO infusion in the nucleus accumbens also increased the consumption of olestra, a palatable non-caloric fat substitute (Katsuura et al., 2011). The preference for fat intake after DAMGO administration was blocked by systemic or intra-accumbens naltrexone administration, further validating the influence of nucleus accumbens opioid signaling in modulating the preference for highly palatable food, especially if rich in fats (Zhang et al., 1998). Similar results were also observed with chocolate flavored pellets and banana flavored pellets. DAMGO infused rats preferred both pellets when they were presented separately, but when given the choice **DAMGO-infused** rats preferentially chose the chocolate flavored ones (Woolley et al., 2006). Similarly, the infusion of DAMGO into the nucleus accumbens also increased the intake of salt and saccharin solution, without altering the intake of water (Zhang and Kelley, 2002). Unlike DAMGO, the infusion of Met-enkephalin, of its synthetic analog [D-Ala²] Met-enkephalin (DALA) and of the DOR-specific

ligand [D-Pen2, Pen5]-enkephalin (DPDPE), had however no significant effects on fat intake (Katsuura and Taha, 2010); and DAMGO in combination with DPDPE had a suppressive effect on feeding (Katsuura and Taha, 2010).

When morphine itself was injected at different levels in the nucleus accumbens, it was observed that its infusion in the shell of the nucleus accumbens increased food intake more than an infusion in the core (Pecina and Berridge, 2000), highlighting some anatomical specificity. Furthermore, within the medial nucleus accumbens shell, microinjections of DAMGO in its rostradorsal region revealed specialized opioid hedonic hotspots which showed positive hedonic orofacial reactions to sucrose taste (Castro and Berridge, 2014; Pecina and Berridge, 2005; Smith and Berridge, 2007), while microinjections of opioids in the caudal nucleus accumbens shell highlighted the presence of “coldspots” favoring hedonic suppression (Castro and Berridge, 2014). Looking for the local actors contributing to the nucleus accumbens opioid influence on fat intake, various receptors were locally co-manipulated. Antagonism of D₁ receptors, D₂ receptors, AMPA receptors and cholinergic receptors prior to the infusion of DAMGO was compared to pretreatment with naltrexone, and it was observed that only antagonism of muscarinic receptors with scopolamine reduced DAMGO-induced fat intake (Perry et al., 2009; Perry et al., 2014; Will et al., 2006). While these data support the presence of a cholinergic-opioid interaction, it should be mentioned that the local stimulation of the cholinergic system alone is insufficient to increase fat intake; *i.e.* the bilateral co-infusion of acetylcholine and of the cholinesterase inhibitor physostigmine in the nucleus accumbens did not affect the intake of fat diet (Will et al., 2006). A similar interaction was also found for the accumbens adenosine and opioid system in the regulation of feeding. Inhibition of adenosine signaling in the nucleus accumbens of rats, using the A_{2A} receptor antagonist MSX-3, increased DAMGO-induced high-fat feeding, while no effect was observed with adenosine agonists (Pritchett et al., 2010). Lastly, rats with *ad libitum* access to standard chow and exposure to intermittent bouts of sweetened fat, predator stress or intraccumbal shell infusion of DAMGO or amphetamine, were challenged with intraaccumbal shell infusion of muscimol and studied for feeding. Among these various conditions, only the repeated exposure to sweetened fat or the repeated DAMGO infusion in the nucleus accumbens sensitized muscimol-induced feeding (Newman et al., 2013), suggesting that

palatable food intake could drive opioid-mediated neuroadaptations in GABA signaling within the nucleus accumbens.

3.2 *Circuitry involved in opioid effects within the nucleus accumbens on feeding*

As shown with GABA manipulation, the effect of opioid manipulation in the nucleus accumbens has been put in a neuroanatomy context, looking for implicated circuits. The increased fat intake following infusion of DAMGO in the nucleus accumbens was for example blocked by concurrent infusion of muscimol in the dorsomedial hypothalamic nucleus, the lateral hypothalamus, the ventral tegmental area, the intermediate region of the nucleus of the solitary tract (Will et al., 2003) or the basolateral or central nucleus of the amygdala (Will et al., 2004), or partially blocked by infusion of naltrexone in the ventral tegmental area (MacDonald et al., 2003). Concerning the amygdala, temporary inactivation of its central nucleus with muscimol decreased the DAMGO-induced high-fat intake and baseline food intake, whereas inactivation of the basolateral amygdala selectively decreased the DAMGO-induced high fat intake without affecting the baseline feeding (Will et al., 2009). This finding with muscimol inhibition of amygdala nuclei was mostly similar to results obtained with naltrexone inhibition of these nuclei. Indeed, pretreatment with naltrexone in the basolateral amygdala also attenuated the increased high fat intake after DAMGO infusion in the nucleus accumbens, without affecting fat intake in 24-hour food-deprived animals that did not receive DAMGO (Parker et al., 2010); whereas naltrexone in the central nucleus of the amygdala may (Kim et al., 2004) or may not (Parker et al., 2014) affect the increased high fat intake in rats infused with DAMGO in the nucleus accumbens, but did decrease fat intake *per se* in 24-hour food-deprived animals without opioid administration in the nucleus accumbens (Parker et al., 2014). Concerning the hypothalamic component of the circuit, both rats treated with the orexin receptor antagonist SB334867 and orexin-deficient mice failed to increase the intake of corn-oil after DAMGO administration in the nucleus accumbens (Zheng et al., 2007), highlighting the role of this cell population in the circuit favoring feeding after nucleus accumbens manipulation. An increased recruitment of cFos in these orexin neurons within the perifornical area of the hypothalamus and in the dopaminergic neurons of the ventral tegmental area was observed after DAMGO infusion in the

nucleus accumbens (Parker et al., 2015; Zheng et al., 2007). Considering these data, it was proposed that nucleus accumbens-lateral hypothalamus projections may drive the consumption of high fat food following intra-accumbens DAMGO infusion, by stimulating hypothalamic orexin neurons which would in turn recruit the ventral tegmental area through orexin signaling (Parker et al., 2015; Zheng et al., 2007). However, the inactivation of the basolateral amygdala with muscimol blocked the cFos increase in the hypothalamus but not in the ventral tegmental area (Parker et al., 2015), suggesting the presence of a more complex circuitry. The dose-dependent DAMGO-induced high-fat feeding after its delivery in the nucleus accumbens was also reduced by either inhibiting endogenous Y1 receptor signaling, as shown with delivery of the NPY/Y1R antagonist 1229U91 in the lateral ventricle or paraventricular nucleus of the hypothalamus, or by stimulating MC3/4 melanocortin receptor-signaling with MTII in the lateral ventricle (Zheng et al., 2010). The nucleus accumbens / lateral hypothalamus interaction may in part be related to the fine control of satiety. Indeed, when studying the firing rates of the lateral hypothalamus neurons before/after DAMGO infusion in rats performing an operant task to obtain a sweetened fat emulsion, it was observed that increased satiety decreased motivation to obtain the sweetened fat and was accompanied by a decrease in lateral hypothalamus neuronal firing (Tandon et al., 2017), whereas DAMGO infused in nucleus accumbens counteracted the effect of increased satiety on both behavioral motivation and lateral hypothalamic firing.

3.3 Conclusion on opioids effects within the nucleus accumbens on feeding

Unlike GABA, opioids within the nucleus accumbens affect palatable (especially fat) feeding, and display specific hotspots and coldspots involved in the hedonic response to sugar. The circuitry mediating opioids' effects within the nucleus accumbens still needs to be unraveled, but it involves at least both the hypothalamus and the amygdala.

4 Conclusion and future directions

The striatum and, especially the nucleus accumbens, is an important hub for promoting food intake and for the control of palatable feeding, particularly of fat. In the last few years, the understanding of the mechanisms controlling the preferential palatable food intake by the nucleus

accumbens has significantly deepened, thanks in part to the technical developments allowing selective neuronal manipulation through chemogenetic or optogenetic approaches. We are however only beginning to explore and understand the detailed circuitry implicated in food intake. Dopamine, GABA, and opioids remain key neurotransmitters underlying the striatal component of this neurocircuitry of feeding. As new molecular and anatomical techniques continue to become available, particularly various strains of transgenic mice/rats that selectively allow labeling or targeting of striatal neurons that express given dopamine, GABA or opioids receptors, it should favor exploration of the precise neural circuits involved in the various aspects of feeding behavior. Moreover, the growing application of optical approaches, fiber photometry and two-photon imaging also promise to yield insights into how neural circuits operate to determine feeding and food preference.

In addition, translation to human situation is of course of crucial importance and human imaging provides essential tools to study the role of these neurotransmitter systems in aberrant feeding behavior leading to obesity. There are now magnetic resonance spectroscopy techniques available to study GABA in the human brain (Hnilicová et al., 2016), and the resolution of imaging techniques evolves quickly further helping to unravel the role of specific brain areas in feeding behavior and palatable feeding in particular. We have, for example, little understanding of how the opioid and dopamine systems respond to fat feeding, or even to infusions of fats directly in the stomach which in animals has been shown to induce striatal dopamine release, and whether these responses are different in obese subjects. It would be important to translate the animal studies that provided insights into the role of these systems into humans to verify whether these are important targets for obesity.

5 Conflict of interest statement

The authors declare no conflict of interest.

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Figure legends

Figure 1. Schematic connectivity of the dorsal striatum (A) and nucleus accumbens (B). To simplify, the illustration does not show all interconnections. The dark red/dark blue fill inside the boxes represents the direct/indirect pathway. The red lines present the main excitatory inputs, the green line the modulatory dopamine input, and the blue lines the inhibitory outputs. The arrows and blunt ends direct toward the output structures. Abbreviations: A2AR, adenosine 2A receptor; D1R, dopamine 1 receptor; D2R, dopamine 2 receptor; LH, lateral hypothalamus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VTA, ventral tegmental area.

Figure 2. Food intake and dopamine. The top half of the panel illustrates striatal modulation of dopamine by food intake, while the bottom half illustrates the consequences of a loss or a rescue of dopamine on general feeding behavior. General food intake increases dopamine release in the striatal complex and palatable or high-fat food intake preferentially favors dopamine release in the nucleus accumbens. Concordantly, loss of dopamine by gene inactivation or 6-OHDA lesion decreases general feeding behavior, which can be restored by pharmacological or viral-mediated rescue. While 6-OHDA lesion of the SNc decreases general feeding behavior, there is evidence that it may also favor a more specific increase in fat intake (Joshi et al., 2021a). Red color highlights an increase, while blue highlights a decrease. Abbreviations: 6-OHDA, 6-hydroxydopamine; DA, dopamine.

Figure 3. Gut and dopamine. Prolonged high-fat food intake suppresses the production of OEA in rats' intestine and decreases the basal dopamine levels in the striatal complex. When OEA levels are restored *via* OEA injections or *via* Roux-en-Y bypass surgery, the action of this lipid messenger on the PPAR- α receptor favors an increase in basal dopamine levels in the striatal complex and a decrease of appetite for high-fat food. Abbreviation: OEA, oleoylethanolamine.

Figure 4. Food intake and dopamine signaling. The left and right halves of the panel respectively illustrate human and rodent studies. Taq1A polymorphism favors risk of obesity. In general, obesity and high fat food intake lead to a decrease in D1R, D2R and DAT in the dorsal striatum and the nucleus accumbens, although some studies report controversial results especially concerning D2R. Circles represent the proportion of studies: red color highlighting an increase, blue a decrease, and grey no change. Abbreviations: D1R, dopamine receptor D1; D2R, dopamine receptor D2; DAT, dopamine transporter.

Table 1: The dopamine system and feeding behaviors

Species/sex	Experiment	Effect	Reference
Albino rats, ♂	food deprived feeding	↗ DOPAC in NAc, Hyp and Amy	(Heffner et al., 1980)
Obese (<i>falfa</i>) Zucker rats		↘ D ₂ R in striatum	(Hamdi et al., 1992)
C57BL/6 mice, ♂	cDIO / cDR / LF	↗ D ₂ R mRNA in NAc with cDIO ↘ D ₂ R in rostral CP with cDIO	(Huang et al., 2005) (Huang et al., 2006)
C57BL/6 mice, ♂	HFD or LFD for 20 days	↗ D ₂ R and ↘ DAT density in CP ↗ D ₂ R binding in NAc shell	(South and Huang, 2008)
Wistar rats, ♂	obese due to extended access to palatable high-fat food	↘ D ₂ R in striatum	(Johnson and Kenny, 2010)
SD rats, ♂; Wistar rats, ♂	HFHS diet	↗ D ₂ R in striatum ↘ D ₁ R in NAc	(Alsio et al., 2010)
C57BL/6 mice, ♂	HFD for 12 weeks	↗ D ₂ R, BDNF and ΔFosB, ↘ D ₁ R in the NAc	(Sharma and Fulton, 2013)
Long-Evans rats, ♂	HFD	↘ D ₂ R in ventral striatum	(Adams et al., 2015)
SD rats, ♂	bilateral 6-OHDA lesion of SNc and Hyp	rats display aphagia and adipsia	(Ungerstedt, 1971)
SD rats, ♂	DA agonists and antagonists in rats with ICV 6-OHDA	↘ food intake	(Heffner et al., 1977)
Rats	dopamine injected in NAc and striatum	↗ food and water intake	(Pal and Thombre, 1993)
Wistar rats, ♂	bilateral 6-OHDA lesion of NAS and OT	↗ food intake in 23-hr food deprived rats	(Koob et al., 1978)
SD rats, ♀	bilateral radiofrequency lesions of SNc	does not produce aphagia and adipsia	(Hodge and Butcher, 1980)
DD mice	feeding behavior	presence of aphagia and adipsia	(Zhou and Palmiter, 1995)
DD mice	rAAVs mediated rescue of dopamine	reversal of aphagia and adipsia	(Szczyпка et al., 2001)
DD mice	pharmacological and CAV-2 cre mediated rescue of dopamine	reversal of aphagia and adipsia	(Hnasko et al., 2006; Sotak et al., 2005)
SD rats, ♂	6-OHDA lesion of SNc and INAc	↘ chow intake with SNc lesion; ↗ fat intake with SNc and INAc lesion	(Joshi et al., 2021a)
Wistar rats, ♂	lentivirus mediated knockdown of D ₂ R	↗ palatable high-fat food intake	(Johnson and Kenny, 2010)
C57BL/6 mice, ♂	OEA given to high fat fed mice	OEA restores gut-stimulated dopamine release	(Tellez et al., 2013)
C57BL/6J mice	global D ₂ R KO	↔ food intake and weight	(Beeler et al., 2016)
Transgenic D ₂ R-OE mice and littermates	mouse model of D ₂ R overexpression	↘ BAT thermogenesis, ↘ energy expenditure, and ↗ obesity despite reduced eating	(Labouesse et al., 2018)
D ₁ R-KO mice	HFHS diet genetic rescue of D ₁ R in SCN and NAc	animals resistant to DIO SCN rescue only restores diet induced overconsumption	(Grippo et al., 2020)
Lister Hooded rats, ♂	raclopride (0.1, 0.3, and 1 mg/kg) i.p.	↗ food intake at low dose ↘ food intake at high dose	(Clifton et al., 1991)
SD rats, ♂	raclopride (50, 200, 400, and 800 nmol/kg) s.c.	↗ fat intake at low dose ↘ fat intake at high dose	(Baker et al., 2001)
SD rats, ♂	raclopride (0, 1, 2 μg/0.5μL/side) in NAc core and shell	↔ food intake	(Baldo et al., 2002)
Long Evans rats, ♂	dopamine antagonists in NAc SCH23390 (0.1, 1.0, 2.0 μg/0.5μL/side and raclopride (0.2, 2.0, and 4.0 μg/0.5μL/side)	↔ food intake	(Lardeux et al., 2015)
SD rats, ♂	SCH23390 (1 μg/0.5 μL/side) and raclopride (1 μg/0.5 μL/side) pretreatment in NAc before DAMGO	↔ food intake	(Will et al., 2006)
Lister Hooded rats, ♂	SCH23390 (0.01, 0.03, and 0.1 mg/kg) s.c.	↘ food intake	(Clifton et al., 1991)
Rats	systemic SCH23390 (0.01, 0.03, 0.05 and 0.1 mg/kg) s.c	↘ water consumption	(Clifton et al., 1991; Gilbert and Cooper, 1987; Ljungberg, 1989)
SD rats, ♂	SCH23390 (50, 200, 400, and 800 nmol/kg) s.c.	↔ food intake	(Baker et al., 2001)
Wistar rats, ♀	SCH23390 (3.24, 324 pg/μL/min for 6h) in NAc	↔ food intake, ↘ water consumption	(Inoue et al., 1995)
Wistar rats, ICR mice, ♂	SCH23390 (200 ng/0.2μL/side) in LH	↔ food intake	(Yonemochi et al., 2019)
Zucker/SD rats, ♂	obese (<i>falfa</i>), lean (<i>falfa</i>) Zucker rats and DIO rats treated with 10 mg/kg bromocriptine	↘ food intake and body fat ↗ D ₂ R (<i>falfa</i>) but not in DIO rats ↗ DAT in DIO rats but not (<i>falfa</i>)	(Davis et al., 2009)
Wistar rats, ♂	DIO rats	tesofensine ↘ D _{2/3} R in NAc	(van de Giessen et al.,

SD rats, ♂	tesofensine (2.0 mg/kg) SCH23390 (0.6 µg/0.5 µL/side) in INAc raclopride (1 µg/0.5 µL/side) in INAc	∨ food intake, ∨ weight gain ↗ fat intake in free choice HFHS diet ↔ in food intake in free choice HFHS diet	2012) (Joshi et al., 2021b)
Albino rats, ♂	bromocriptine (15, 30 and 60 mg/kg), quinpirole (0.05, 0.2, 0.8 and 1.6 mg/kg) and SKF38393 (10, 30, 50 mg/kg) i.p	dose dependent anorexia	(Zarrindast et al., 1991)
Rats	systemic SKF38393 (0, 1, 3, 5, 10, 20 mg/kg.)	∨ food intake at high dose	(Cooper et al., 1992; Cooper et al., 1990; Gilbert and Cooper, 1985; Martin- Iverson and Dourish, 1988; Rusk and Cooper, 1989)
Rats	SKF38393 (1, 3 and 10 mg/kg) s.c.	↗ food intake at low dose ∨ food intake at high dose	(Cooper and Al-Naser, 2006; Cooper et al., 1992)
Hooded rats, ♂	SKF38393 (1, 3 and 10 mg/kg) s.c. quinpirole (0.03, 0.1 and 0.3 mg/kg) s.c.	SKF 38393 ↗ preference of HFHS. Quinpirole ∨ preference of HFHS	(Cooper and Al-Naser, 2006)
Hooded rats, ♂	SKF38393 (0.01, 0.1, 1.0 µg/µL) in NAc	↔ food intake	(Phillips et al., 1995)
Wistar rats, ♂	SKF38393 (0.3, 0.6, 1.2, and 5 µg/0.3µL) in PVN	↗ food intake	(Mirmohammadsadeghi et al., 2018)
Zucker rats	bromocriptine 10 mg/kg i.p.	∨ food intake	(Davis et al., 2009; Davis et al., 2006)
Wistar rats, ♂	bromocriptine 80 µg/10µL ICV	↗ food intake	(Evans and Eikelboom, 1987)
Wistar rats, ♀	bromocriptine (0.0025, 0.25, 25 µg/µL for 6h) in NAc	↗ food intake	(Inoue et al., 1997)
Human, 12♂, 8♀ Human, 76♀	PET-(¹¹ C) raclopride fMRI	∨ striatal D ₂ R in obese individual individual with taq1A allele is likely to become obese with ∨ D ₂ R	(Wang et al., 2001) (Stice et al., 2008)
Human, 11♂, 11♀	PET-(¹¹ C) raclopride	∨ striatal D ₂ R ↗ activation of prefrontal areas	(Volkow et al., 2008)
Human, 26♀	Rm fMRI	↗ weight gain ∨ striatal response to palatable food	(Stice et al., 2010)
Human, 30♀	[¹²³ I]IBZM SPECT	∨ striatal D _{2/3} R in obese women	(de Weijer et al., 2011)
Human, 30♂, 30♀	fMRI	adolescents with high risk for obesity show greater activation in CP with food intake.	(Stice et al., 2011)
Wistar rats, ♂	normal-weight adolescents at high/low risk of obesity (¹²³ I)-IBZM imaging on 29 th day HFHS for 28 days	∨ D _{2/3} R availability in NAc	(van de Giessen et al., 2013)
Human 30(22♀/8♂)	PET (N-[¹¹ C]methyl)benperidol	↔ D _{2/3} R in obese	(Eisenstein et al., 2013)
Human 43(22♀/21♂)	[¹⁸ F] fallypride	↗ D _{2/3} R in dorsal and lateral striatum of obese individual	(Guo et al., 2014)
Human 27♀	PET-(¹¹ C) raclopride	↔ D _{2/3} R in obese	(Karlsson et al., 2015)
SD rats	microdialysis and LCMS	consumption of HFHS diet produces different neuroadaptations in mesolimbic neurons	(Vollbrecht et al., 2016)
Human, 33♂, 9♀	PET [¹¹ C](+)-PHNO	↗ D _{2/3} R in obese individual	(Gaiser et al., 2016)

♀, female; ♂, male; 6-OHDA, 6-hydroxydopamine; Amy, amygdala; BAT, brown adipose tissue; BDNF, brain derived neurotrophic factor; CAV-2, canine adenovirus type 2; cDIO, chronic diet induced obesity; cDR, chronic diet resistant; CP, caudate putamen; DA, dopamine; D₁R, dopamine receptor 1; D₂R, dopamine receptor 2; DAT, dopamine transporter; DIO, diet induced obesity; DOPAC, 3,4-dihydroxyphenylacetic acid; fMRI, functional magnetic resonance imaging; HFD, high fat diet; HFHS, high-fat high-sugar; Hyp, hypothalamus; i.p., intraperitoneal; ICV, intracerebroventricular; KO, knock out; LFD, low fat diet; LH, lateral hypothalamus; INAc, lateral nucleus accumbens; NAc, nucleus accumbens; NAS, nucleus accumbens septi; OEA, oleoylethanolamine; OT, olfactory tubercle; PET, positron emission tomography; PVN, paraventricular nucleus; rAAV, recombinant adeno-associated virus; s.c., subcutaneous; SD, Sprague Dawley; SCN, suprachiasmatic nucleus; SNC, substantia nigra pars compacta; SPECT, single-photon emission computed tomography.

Table 2: GABAergic transmission and feeding behaviors

Species/sex	Experiment	Effect	Reference
SD rats, ♂	muscimol (0, 10, 20, 50, or 100 ng/0.5µL/side) in NAcSh	↗ food intake dose dependently	(Stratford and Kelley, 1997)
SD rats, ♂	muscimol (20, 50 ng/0.5µL/side) in different subregions within NAc	↗ food intake in mNAc ↔ food intake INAc & vNAc	(Basso and Kelley, 1999)
SD rats, ♂	muscimol (50, 100 ng /0.5 µL/side) in NAcSh and GABA _A / glutamate antagonist in LH	muscimol ↗ chow intake with cFos-IR in LH, blocked by NMDA antagonist AP-5 in LH	(Stratford and Kelley, 1999)
SD rats, ♂, ♀	muscimol (0.075, 0.1 µg/0.5µL/side) in mNAcSh	↗ food intake	(Soderpalm and Berridge, 2000)
SD rats, ♂	GABA and mu-opioid agonist/antagonist in NAcSh	opioid and GABA agonist ↗ food intake	(Znamensky et al., 2001)
SD rats, ♂	muscimol (25 ng/0.5µL) in NAc or VTA and different opioid antagonists in NAc or VTA	muscimol ↗ food intake, blocked with opioid receptor antagonism	(Khaimova et al., 2004)
SD rats, ♂	muscimol (75 ng/0.5µL/side) in NAc and NPY1 antagonist (0, 5, 30 µg/4µL) i.c.v.	muscimol ↗ food intake, blocked with NPY1 antagonist	(Stratford and Wirtshafter, 2004)
SD rats, ♂	muscimol (25 ng/0.5µL) in NAc and inactivation of amygdala	inactivation of amygdala ↘ muscimol induced feeding	(Baldo et al., 2005)
Long Evans rats, ♂	muscimol (50 ng/0.5µL/side) in NAc	GABA stimulation ↗ general food intake	(Woolley et al., 2006)
SD rats, ♂	rats kept on operant conditioning	muscimol ↗ operant responding for food	(Stratford and Wirtshafter, 2012)
SD rats, ♂	Muscimol (75 ng/0.5µL/side) and dopamine antagonist [SCH23390 (3 µg/0.5µL/side); raclopride (5 µg/0.5µL/side)] in mNAcSh	no effect of dopamine blockade on muscimol induced food intake	(Richard et al., 2013)
SD rats, ♂	muscimol, baclofen, bicuculline and DAMGO in NAcSh and VP	GABA receptors in VP may control fat intake, but not in NAcSh.	(Covelo et al., 2014)
Wistar rats, ♀	muscimol (128, 256 pmol/0.2µL/side) and baclofen (128, 256 pmol/0.2µL/side) in mNAc	↗ fat intake	(Lopes et al., 2007)
Lister Hooded rats, ♂	baclofen (110, 220, 440 pmol/µL) and muscimol (220, 440, 660 pmol/µL) in NAcSh	↗ food intake	(Pulman et al., 2010)
SD rats, ♂	baclofen (0, 19, 37, 94, or 188 ng/0.5µL/side) in NAcSh	↗ food intake dose dependently	(Stratford and Kelley, 1997)
Lister hooded rats, ♂	baclofen in NAcSh	↗ food intake	(Ward et al., 2000)
SD rats, ♂	baclofen (200 µg/0.5µL) in NAc or VTA and different opioid antagonist in NAc or VTA	↗ food intake after baclofen injection with differential blockade after different opioid receptor antagonism at different locations	(Khaimova et al., 2004)
SD rats, ♂	systemic baclofen (1, 1.8 mg/kg) during fat consumption	↘ fat intake	(Avena et al., 2014; Buda-Levin et al., 2005; Rao et al., 2008)
SD rats, ♂	baclofen (100, 200 ng/0.5µL/side) in NAc/VTA and GABA _A /GABA _B antagonist in NAc/VTA	bidirectional GABA _B /GABA _B and unidirectional GABA _B /GABA _A interaction between VTA and NAc	(Miner et al., 2010)
SD rats, ♂	bicuculline (10, 50, 100, or 200 ng/0.5µL/side) in VP	↗ food intake	(Stratford et al., 1999)
SD rats, ♂	intraaccumbal muscimol (20 ng/rat), bicuculline (40 ng/rat) and diazepam (5µg/rat) with haloperidol (0.01 mg/kg/rat/day) i.p.	haloperidol ↗ food intake; ↗ with muscimol and diazepam; ↘ with bicuculline	(Meena et al., 2009)

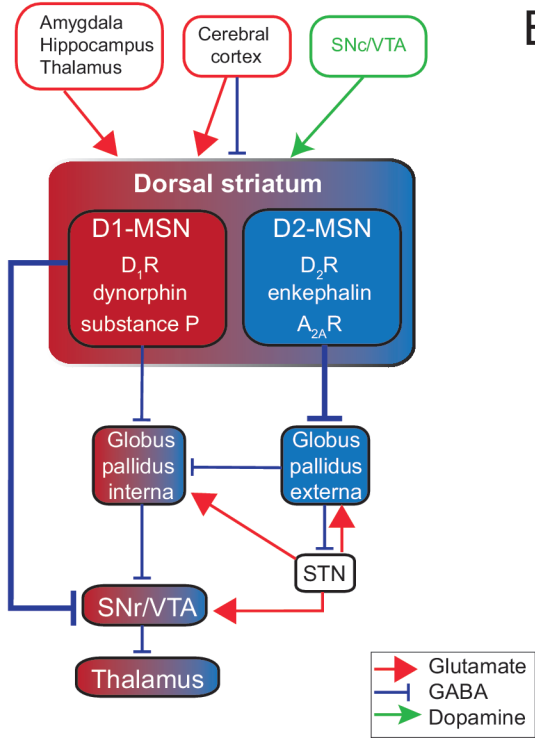
♀, female; ♂, male; GABA, gamma-aminobutyric acid; i.c.v., intracerebroventricular; i.p., intraperitoneal; IR, immunoreactivity; LH, lateral hypothalamus; INAc, lateral nucleus accumbens; mNAc, medial nucleus accumbens; mNAcSh, medial nucleus accumbens shell; NAc, nucleus accumbens; NAcSh, nucleus accumbens shell; NMDA, N-methyl-D-aspartate receptor; NPY, neuropeptide Y; SD, Sprague Dawley; vNAc, ventral nucleus accumbens; VP, ventral pallidum; VTA, ventral tegmental area

Table 3: The opioid system and feeding behaviors

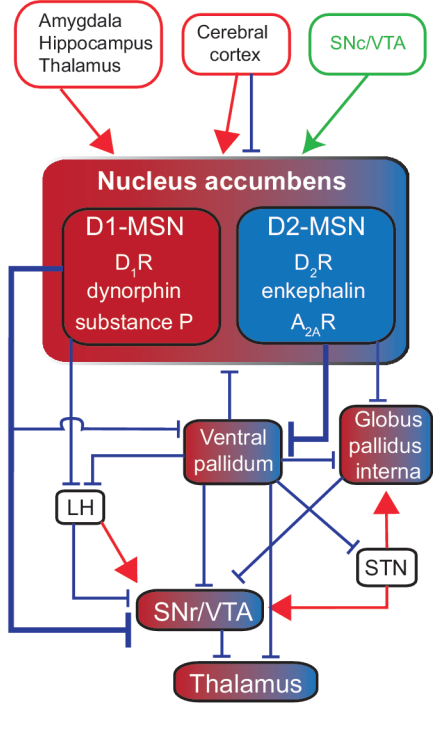
Species/sex	Experiment	Effect	Reference
Long Evans hooded rats, ♂	morphine (1, 2.5, 5 mg/kg s.c.) and naloxone (0.5, 1, 2.5 mg/kg s.c.)	morphine ↗ food intake naloxone ↘ food intake	(Jalowiec et al., 1981)
Wistar Rats, ♂	opioid receptor agonist (1, 2, 5, 10 nmol/μL/side) in NAS	↗ food intake dose dependently	(Majeed et al., 1986)
SD rats, ♂	morphine (0.01, 0.1, 1, 10 nmol/μL/side) in NAc and VTA	↗ food intake; more effect observed in NAc	(Mucha and Iversen, 1986)
Rats, ♂	DAMGO (0.025, 0.25, 2.5 μg/0.5μL/side) in NAc and NTX (5 mg/kg i.p.)	↗ food intake reversed by NTX	(Bakshi and Kelley, 1993)
Swiss mice, ♂	morphine (25 mg/kg s.c.)	↗ food intake with L-arginine	(Calignano et al., 1993)
SD rats, ♂	opioid antagonists in NAc naloxone (1, 10, 30 μg/μL/side) NTX (0.2, 2, 20 μg/μL/side) BFNA (15 μg/μL/side) naloxonazine (10 μg/μL/side) NTI (1, 10, 20 μg/μL/side) nor-BNI (0.1, 1, 10 μg/μL/side)	↘ sucrose intake	(Kelley et al., 1996)
SD rats, ♂	DAMGO (0.025, 0.25, 2.5 μg/0.5μL/side), NTX (20 μg/μL/side) in NAc and NTX (5 mg/kg i.p.)	↗ fat intake selectively	(Zhang et al., 1998)
SD rats, ♂	DAMGO (0.025, 0.25, 2.5 μg/0.5μL/side) at different levels in NAc and striatum	↗ fat intake dose dependently in NAc	(Zhang and Kelley, 2000)
SD rats, ♂	morphine (0.5μg/0.25-0.5μL/side) at different levels in NAc	↗ food intake more in shell than core	(Pecina and Berridge, 2000)
SD rats, ♂	DAMGO (0.025, 0.25 μg/0.5μL/side) in NAc	↗ intake of saccharin, salt, and ethanol	(Zhang and Kelley, 2002)
SD rats, ♂	DAMGO (0.1, 0.3, 1, 3 nmol/0.5μL/side) and NTX (2.5, 5, 25μg/0.5μL/side) in NAc or in VTA	DAMGO ↗ food intake when infused in NAc or VTA; blocked by NTX in opposite area	(MacDonald et al., 2003)
SD rats, ♂	DAMGO (2.5 μg/0.5μL/side) and NTX (1.25, 2.5, 5μg/0.5μL/side) in NAc or in CeA	DAMGO induced food intake blocked with NTX in contrary site	(Kim et al., 2004)
SD rats, ♂	DAMGO (0.01, 0.1 μg/0.2μL/side) at different levels in NAc	↗ food intake; rostradorsal region of medial shell mediates hedonic response to sucrose	(Pecina and Berridge, 2005)
Dutch belted Rabbits, ♂	irreversible MOR antagonist, BFNA (8 nmol/0.8μL/side) in NAc	↘ in sucrose intake	(Ward et al., 2006)
Long Evans rats, ♂	naloxone (0.1 μg/0.25μL) in NAcSh, (0.1 μg/0.5μL) in VP, BLA, and CeA	opioids in NAcSh/VP mediate palatability while in BLA it mediates incentive value for sucrose	(Wassum et al., 2009)
SD rats, ♂	DAMGO (0.25 μg/0.5μL/side) in NAc and NTX (5 μg/0.25 μL/side) in BLA	NTX blocked ↗ high fat in DAMGO infused rats but not in 24hrs food deprived	(Parker et al., 2010)
SD rats, ♂	DAMGO (0.25 nmole/0.5μL/side) in NAc	DAMGO in NAc ↗ intake of a non-caloric fat substitute	(Katsuura et al., 2011)
SD rats, ♂	opioid receptor antagonists [NTX (0.05, 0.5, 2.5 μg/0.5μL/side)], mu [BFNA (0.2, 2 μg/0.5μL/side)], kappa [NBNI (0.6, 3 μg/0.5μL/side)] or delta [NTI (0.2, 2 μg/0.5μL/side)], with baclofen (100 ng/0.5μL/side) in VTA and NAc	food intake due to baclofen is blocked either unidirectionally or bidirectionally with different opioid receptor antagonism	(Miner et al., 2012)
SD rats, ♂	different opioid receptor agonists at different levels in NAc DAMGO (0.05 μg/0.2 μL/side) DPDPE (3.1 μg/0.2μL/side) U50488H (0.186 μg/0.2 μL/side)	rostradorsal hotspots and caudal coldspots for hedonic response are present within the medial shell of NAc	(Castro and Berridge, 2014)
Long Evans rats, ♂	MOR agonist/antagonist in NAc shell NTX (1, 10, 50 μg/μL/side) BFNA (2.5 μg/μL/side) NTI (0.5, 5, 10 μg/μL/side)	opioid antagonist ↘ sucrose intake in operant conditioning	(Katsuura and Taha, 2014)
SD rats, ♂	DAMGO (0.25 μg/0.5μL/side) in NAc and NTX (5 μg/0.25μL/side) in CeA	NTX blocked ↗ high fat in 24hrs food deprived but not in DAMGO infused rats	(Parker et al., 2014)
SD rats, ♂	rats kept on operant conditioning	DAMGO ↗ operant responding for food	(Stratford and Wirtshafter, 2012)
SD rats, ♂	SCH23390 (1 μg/0.5μL/side), raclopride (2 μg/0.5μL/side), LY293558 (0.01, 0.1 μg/0.5μL/side), scopolamine (0.1, 1, 10 μg/0.5μL/side), and mecamlamine (10 μg/0.5μL/side) pretreatment in NAc before DAMGO (0.25 μg/0.5μL/side)	scopolamine only ↘ DAMGO induced food intake	(Will et al., 2006)
SD rats, ♂	DAMGO (0.25 μg/0.5μL/side) and scopolamine (1, 10 μg/0.5μL/side) in NAc	scopolamine ↘ DAMGO mediated intake of fat	(Perry et al., 2009)
SD rats, ♂	DAMGO (0.25 μg/0.5μL/side) and	DAMGO and scopolamine have opposite	(Perry et al., 2014)

	scopolamine (1, 5, 10 µg/0.5µL/side) at various location in striatum	action on food intake only in NAc core	
SD rats, ♂	GABA and MOR agonist/antagonist in NAcSh	GABA antagonists differentially affect feeding elicited by MOR agonists	(Znamensky et al., 2001)
SD rats, ♂	DAMGO (0.5 µg/0.5µL/side) and muscimol (5, 10 ng/0.25µL/side) in NAc, LH, DMH, VTA, NTS, or dHC	muscimol ∨ DAMGO induced feeding, mu receptor mediated food intake in NAc is dependent on various brain regions	(Will et al., 2003)
Long Evans rats, ♂	DAMGO (0.25 µg/0.5µL/side), muscimol (50 ng/0.5µL/side) and naltrexone (20 µg/0.5µL/side) in NAc	DAMGO infused animal preferred high palatable food in choice paradigm	(Woolley et al., 2006)
SD rats, ♂	DAMGO (0.25 µg/0.5µL/side) in NAc and muscimol (20 ng/0.25µL/side) in BLA/CeA	amygdala is involved in modulating fat intake through DAMGO in NAc	(Will et al., 2009)
SD rats, ♂	DAMGO (2.5 µg/0.5µL/side) and amphetamine (2, 10 µg/0.5µL/side) in NAcSh challenged with muscimol (10 ng/0.5µL/side) with rat on sweetened fat	exposure to sweetened fat and DAMGO infusion in NAc sensitizes muscimol induced feeding	(Newman et al., 2013)
SD rats, ♂	DAMGO (0.25 µg/0.5µL/side) in NAc and muscimol (20 ng/0.5µL/side) in BLA	DAMGO ↗ cFos activation in orexin neurons in Hyp, which is blocked by muscimol in BLA while ↗ cFos activation in DA neurons in VTA is not blocked by muscimol in BLA	(Parker et al., 2015)
SD rats, ♂; & C57BL/6J mice, ♂	DAMGO (0.25 µg/0.5µL/side) in NAc and orexin-1 receptor antagonist SB334867 (30, 60, 100 nmol/3µL/side in LV; 15 nmol/0.5µL/side in VTA)	orexin-1 antagonist ∨ high fat intake in DAMGO treated animals	(Zheng et al., 2007)
SD rats, ♂	adenosine receptor agonist and DAMGO (0.025 µg/0.25µL/side) in NAc	MSX-3 ↗ food intake and locomotor activity	(Pritchett et al., 2010)
SD rats, ♂	DAMGO (0.25 µg/0.5µL/side) in NAc and Y1R antagonist (0.5, 1, 10 µg/3µL/side)/ MC3/4R (0.02, 0.1, 0.5 µg/3µL/side) agonist in LV	Y1R antagonism and MC3/4R agonism ∨ DAMGO mediated high fat intake	(Zheng et al., 2010)
<small>♀, female; ♂, male; Ach, acetylcholin; BFNA, b̄ta-funaltrexamine; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; DA, dopamine; DAMGO, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin; dHC, dorsal hippocampus; DMH, dorsomedial hypothalamus; GABA, gamma aminobutyric acid; Hyp, hypothalamus; i.p., intraperitoneal; LV, lateral ventricle; MOR, mu opioid receptor; NAc, nucleus accumbens; NAcSh, nucleus accumbens shell; NAS, nucleus accumbens septi; NBNI, norbinaltorphimine; NTL, naltrindole; NTS, nucleus tractus solitarius; NTX, naltrexone; PVN, paraventricular nucleus; s.c., subcutaneous; SD, Sprague Dawley; VMH, ventromedial hypothalamus; VP, ventral pallidum; VTA, ventral tegmental area.</small>			

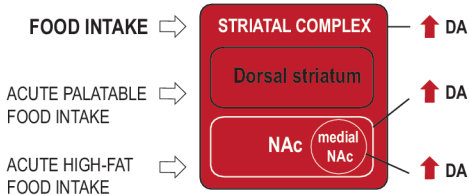
A



B



FOOD INTAKE AND DOPAMINE

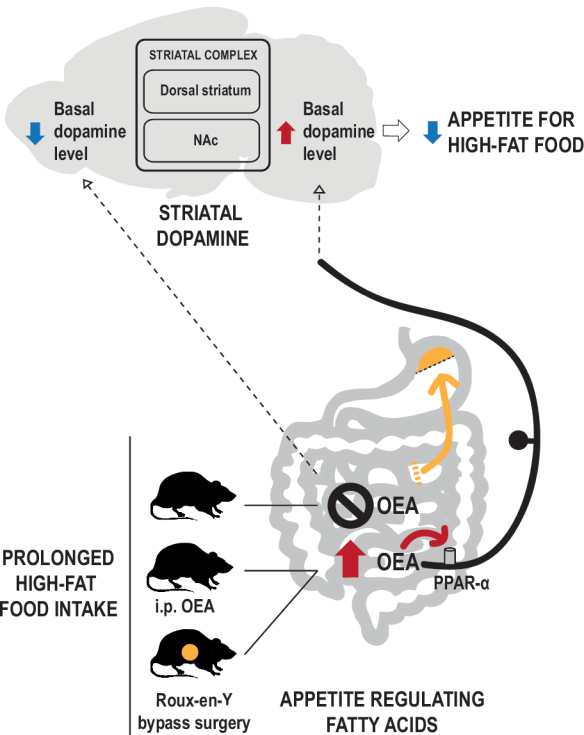


DOPAMINE AND FOOD INTAKE

DA LOSS | 6-OHDA lesion of the SNc
DA-deficient mice ⇒ ↓ **FEEDING BEHAVIOR**


DA RESCUE | L-DOPA administration
Pharmacological approach ⇒ ↑ **FEEDING BEHAVIOR**
Viral approach

DOPAMINE AND GUT



FOOD INTAKE AND DOPAMINE SIGNALING

Human studies  OBESITY
OBESITY PREDISPOSITIONS

Rodent studies  OBESITY
HIGH-FAT FOOD
HIGH-FAT/SUGAR FOOD
HYPERPHAGIA

Obesity



D₂R

STRIATAL COMPLEX

Dorsal striatum

NAc

D₂R




DAT



D₁R



D₂R

 *DRD2/ANKK1* Taq1A polymorphism



 Obesity predispositions