Themed Section: Animal Models in Psychiatry Research

REVIEW

Pharmacological manipulations in animal models of anorexia and binge eating in relation to humans

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Drug/molecular target nomenclature throughout this manuscript conforms to BJP's Guide to Receptors and Channels (Alexander *et al.*, 2013a–c).

Eating disorders, such as anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorders (BED), are described as abnormal eating habits that usually involve insufficient or excessive food intake. Animal models have been developed that provide insight into certain aspects of eating disorders. Several drugs have been found efficacious in these animal models and some of them have eventually proven useful in the treatment of eating disorders. This review will cover the role of monoaminergic neurotransmitters in eating disorders and their pharmacological manipulations in animal models and humans. Dopamine, 5-HT (serotonin) and noradrenaline in hypothalamic and striatal regions regulate food intake by affecting hunger and satiety and by affecting rewarding and motivational aspects of feeding. Reduced neurotransmission by dopamine, 5-HT and noradrenaline and compensatory changes, at least in dopamine D_2 and $5\text{-HT}_{2C/2A}$ receptors, have been related to the pathophysiology of AN in humans and animal models. Also, in disorders and animal models of BN and BED, monoaminergic neurotransmission is down-regulated but receptor level changes are different from those seen in AN. A hypofunctional dopamine system or overactive α_2-adrenoceptors may contribute to an attenuated response to (palatable) food and result in hedonic binge eating. Evidence for the efficacy of monoaminergic treatments for AN is limited, while more support exists for the treatment of BN or BED with monoaminergic drugs.

LINKED ARTICLES

This article is part of a themed section on Animal Models in Psychiatry Research. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-20

Abbreviations

SERT, 5-HT (serotonin) transporter; ABA, activity-based anorexia; AN, anorexia nervosa; BED, binge eating disorder; BMI, body mass index; BN, bulimia nervosa; DAT, dopamine transporter; HVA, homovanillic acid; LHA, lateral hypothalamus; NET, noradrenaline transporter; RWA, running wheel activity; SIH, stress-induced hyperactivity; SSRI, selective 5-HT (serotonin) reuptake inhibitor; THC, Δ^9-tetrahydrocannabinol; VMH, ventromedial hypothalamus; VMN, ventromedial nucleus

Table of Links

Targets	Ligands	
5-HT$_{1A}$ receptor	5-HT	Olanzapine
5-HT$_{1B}$ receptor	Dopamine	Pimozide
5-HT$_{2A}$ receptor	Noradrenaline	Quetiapine
5-HT$_{2C}$ receptor	Amphetamine	Reboxetine
5-HT$_3$ receptor	α-MSH	Risperidone
5-HT$_4$ receptor	Aripiprazole	Sertraline
5-HT$_6$ receptor	Bupropion	Sibutramine
α$_1$ adrenoceptor	meta-Chlorophenylpiperazine	Sulpiride
α$_2$ adrenoceptor	Chlorpromazine	Δ9-tetrahydrocannabinol, THC
β$_2$ adrenoceptor	Cyproheptadine	Topiramate
CRF$_1$ receptor	DAMGO	
Dopamine D$_1$ receptor	Desipramine	
Dopamine D$_2$ receptor	Fenfluramine	
Dopamine D$_3$ receptor	Fluoxetine	
Dopamine D$_4$ receptor	cis-Flupenthixol	
Ghrelin receptor (GHS-R1a)	Fluvoxamine	
μ opioid receptor	Ghrelin	
Melanocortin MC$_1$ receptor	Haloperidol	
NET, noradrenaline transporter	Leptin	
SERT, 5-HT transporter	Neuropeptide Y	

This Table lists the protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson et al., 2014) and the Concise Guide to PHARMACOLOGY 2013/14 (Alexander et al., 2013a–c).

Introduction

Eating disorders are conditions defined by significant disturbances in eating behaviour or behaviours intended to control body weight, which impair physical and mental health. Various types of eating disorders exist, among which are anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorders (BED). Some researchers suggest that AN and BN are two phases of the same disorder because majority of AN patients have episodes of bingeing and purging with a majority of BN patients starting with a short episode of starvation (Eddy et al., 2002; Södersten et al., 2006). Indeed, there is a high rate of crossover between the AN and BN diagnosis (Klump et al., 2001; Eddy et al., 2008; Peat et al., 2009). Nevertheless, the subdivision within eating disorders is clinically relevant as the subtypes differ in treatments, their effectiveness, medical complications and prognosis.

The progress in the treatment of eating disorders requires deepened understanding of their pathophysiology and symptoms. Although psychological and environmental factors play a pivotal role in the development of eating disorders, a better understanding of the biological basis that underlies the pathophysiology and symptomatology of eating disorders may help in the development of suitable pharmacological and psychological treatments. As the investigation of these aspects of eating disorders is difficult or impossible in humans, animal models are essential to study certain aspects of eating disorders in a controlled genetic and environmental manner. This review will cover animal models of eating disorders, their relation to humans and a description of pharmacological manipulations in animal models and humans.

Concepts of food intake

Richter's classic experiments indicated that food and water intake in all mammals is episodic, not continuous (Richter, 1922). Episodes of feeding and drinking result from ongoing interactive mechanisms, which either stimulate these behaviours (hunger, thirst) or restrain them (satiety and satiation). In rats, daily food intake occurs in series of meals separated by intermeal intervals and overall intake consists of two components, meal size and meal frequency (Rosenwasser et al., 1981). These two components can be separately manipulated, suggesting regulation via separate physiological processes (Rosenwasser et al., 1981).

Rats display a circadian rhythm in active feeding behaviour and the majority of intake occurs during the dark period,
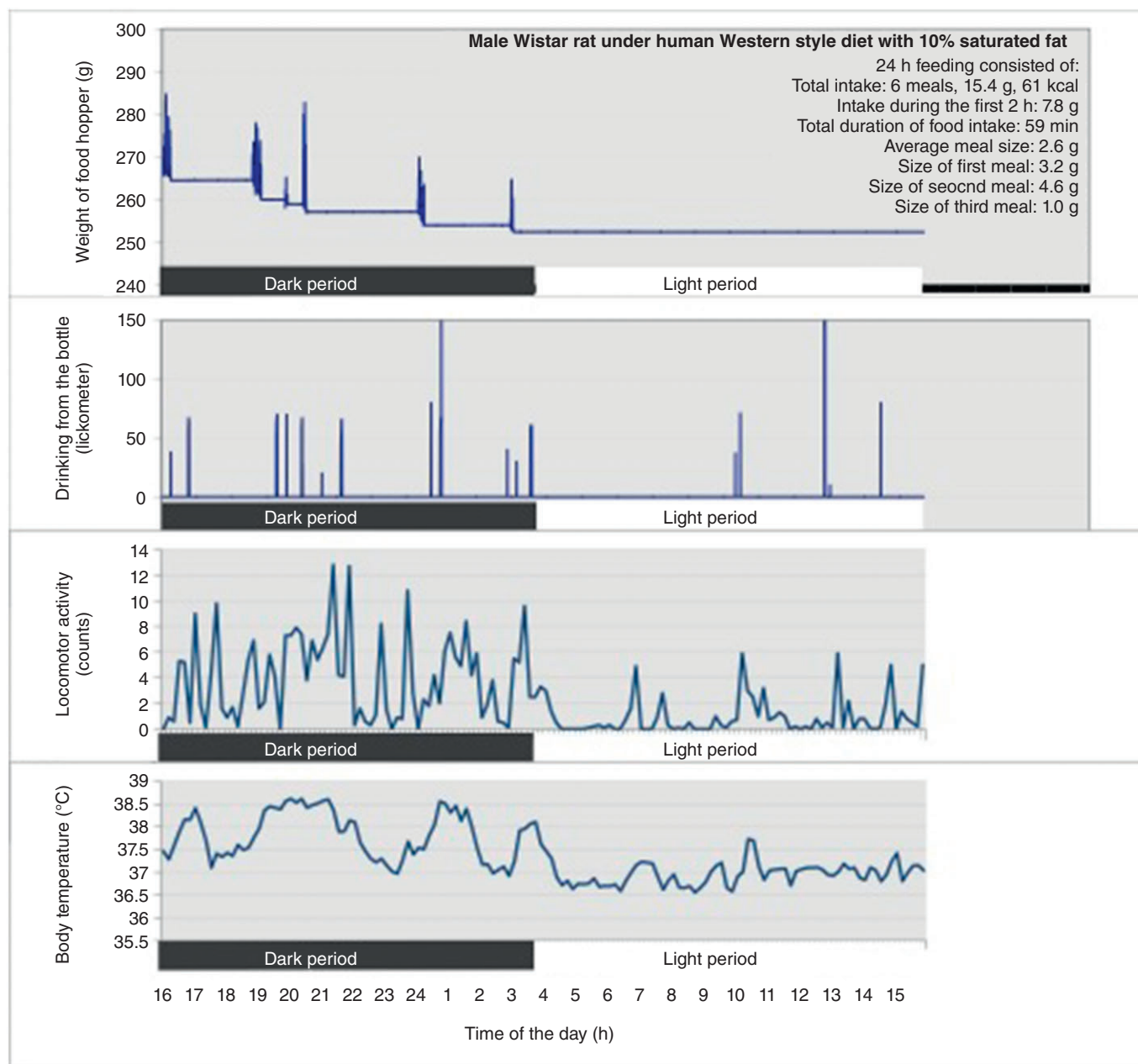
Figure 1
Example of 24 h behavioural data from one naïve male Wistar rat using automated monitoring system. Food intake was detected by automated weighing of the food hopper and water intake was measured by recording the animal's contact with bottle nipple by lickometer. Each burst represents a meal or drinking session. Locomotor activity (counts) and core body temperature (°C) were measured by telemetric transmitters. All data were recorded to a computer. Dark bar represents the dark period (lights off, 16:00–04:00 h) and light bar represents the light period (lights on, 04:00–16:00 h).

after which food intake is minimal until occasional meals are again consumed during the latter part of the light phase (Figure 1) (Rosenwasser *et al.*, 1981; Janhunen *et al.*, 2011). Meal size is positively correlated with the duration of post-meal interval (Thomas and Mayer, 1968; Smith, 2000). This postprandial correlation is thought to reflect the action of meal-initiated metabolic events on the induction and maintenance of intermeal satiety.

Monitoring feeding behaviour in animals

Feeding behaviour can be monitored automatically and continuously every few seconds or minutes or by weighing food pellets or mash manually at selected timepoints once or twice per day. Automated monitoring improves throughput and

accuracy of measurements and reduces manual work and stress caused by human interference. Large numbers of animals can be monitored over long periods of time under conditions supporting animals' normal stress-free behaviour.

Unlike manual recording, automatic monitoring records meal patterning, consisting of meal size and meal frequency for each individual animal. Various automated monitoring methods have been used to study feeding behaviour in rodents. There are (i) operant methods, in which the animal presses a bar to obtain the food (Anliker and Mayer, 1956; Snowdon, 1969); (ii) devices which record the presence of either the whole animal inside a feeding chamber (Milner and De Caire, 1965; Madrid et al., 1989) or the animal's head over the food cup (Madrid et al., 1993); (iii) devices which detect the animal's contact with the food, commonly known as eatometers (Fallon, 1965; Kissileff, 1970; Madrid et al., 1995); (iv) pellet-detecting eatometers which deliver a pellet each time one is eaten (Kissileff, 1970; Madrid et al., 1995); and (v) electronic balances which continuously measure the weight of the food and relay the information to a computer (Pokrovsky and Le Magnen, 1963; Hulsey and Martin, 1991; Janhunen et al., 2011; 2013).

The automated electronic food weighing system in rats gives continuous data from an animal's food intake and meal patterning (Tiesjema et al., 2007; de Backer et al., 2010; Janhunen et al., 2011; 2013; la Fleur et al., 2013; Merkestein et al., 2013). A meal is defined as a feeding episode, for example, with a minimal consumption of 0.5 g chow and a 5 min intermeal interval, information is sent every 12 s to a computer. Figure 1 shows an example of a 24 h data from a rat whose feeding, drinking and locomotor behaviour and core body temperature were automatically recorded. A lickometer, which monitors contact with the nipple of a water bottle, was combined with the food weighing system to investigate the animal's drinking behaviour (Figure 1). Telemetric transmitters in the intraperitoneal cavity simultaneously monitored locomotor activity and core body temperature (Figure 1). Feeding behaviour consisted of meals of different sizes and meals were followed by varying intermeal intervals (Figure 1). Figure 1 shows that most feeding behaviour occurred during the dark period and drinking behaviour often followed a meal. The rat was most active during the dark period and particularly at the time when it consumed a meal. Core body temperature rose after these active feeding periods (Figure 1). Automated systems can be used for the monitoring of different components of energy expenditure after various acute or chronic drug treatments (van der Zwaal et al., 2008; Janhunen et al., 2011; 2013) or local injections of compounds in the activity-based anorexia (ABA) model (Verhagen et al., 2009).

Animal models of anorexia

There are at least four models of AN in rodents: (i) the dietary restriction model; (ii) the stress-induced appetite loss; (iii) the stress-induced hyperactivity (SIH) model; and (iv) the ABA model.

The dietary restriction model

There are two ways to achieve food restriction: (i) animals are given access to a fixed percentage of the food that they would normally consume during 24 h; or (ii) food is provided *ad libitum* for a fixed amount of time (Siegfried et al., 2003).

Stress-induced appetite loss

Various acute and chronic stressors may be used to evoke a loss of appetite in experimental animals, including tail pinch, cold swimming, direct brain stimulation or separation stress. Chronic stress results in overfeeding on palatable food; however, short-term stress in particular decreases food intake (Adam and Epel, 2007). Stress can also activate the immune system, which, in turn, can reduce food intake and appetite, a phenomenon commonly described with infections and sickness (Dantzer et al., 2008). Models classified in the category of stress-induced appetite loss are not suitable as models of AN because the limited food intake observed in AN patients does not result from a lack of appetite (Casper et al., 2008). AN patients were found to have no disturbances in appetite and their perception of hunger was similar to controls (Garfinkel, 1974).

The activity-based models target the combination of two AN symptoms: (i) restricted feeding and (ii) high levels of physical activity. These models promote symptoms similar to those in AN patients, including hypophagia, hyperactivity, progressive weight loss and disruptions of the ovarian reproductive cycle. The activity-based models are based on the observation that access to a running wheel causes a transient decrease in food intake in rats and mice (Routtenberg, 1968). Furthermore, the effect on energy expenditure is paradoxically potentiated when running wheel access is combined with dietary restriction, which leads to a further increase in activity levels (Finger, 1951; Hall and Hanford, 1954; Reid and Finger, 1955). Rodents exposed to this combination of factors are not able to compensate for their increased energy expenditure by increasing caloric intake and may eventually starve themselves to death (Routtenberg and Kuznesof, 1967). The phenotype in both activity-based models mimics symptoms of AN that are observed in starving patients. There are, however, also differences between the two models, which we will briefly explain in the succeeding paragraphs.

The SIH model

In this model, rodents have unlimited access to running wheels and receive a fixed percentage of the amount of food they would ingest per day under *ad libitum* conditions (Broocks et al., 1990). There is no time limit on the consumption of the fixed amount of food. Animals receive the same amount of food over the whole experimental period, which prevents the self-starvation observed in the ABA model. The primary focus of the SIH model is the increase of physical activity levels evoked by food restriction, whereas the ABA model emphasizes on the effect of increased activity in anticipation to meals, making the ABA model a more appropriate AN model than SIH (Gutierrez, 2013).

The ABA model

In this model, animals are given access to food for a limited amount of time per day (e.g. 2 h per day for mice and 1 h per

day for rats) (Hall and Hanford, 1954; Routtenberg and Kuznesof, 1967; Dixon *et al.*, 2003). This time is too short for animals to consume the amount of food they would ingest under *ad libitum* conditions. Moreover, in the ABA model, rats exposed to a running wheel will consume even less food than controls (rats without running wheel access) given an equal duration of food access. Interestingly, this is observed if food availability is limited to once per day and the difference in food intake disappears if the number of periods of food availability is increased, even when the total time of food availability remains the same (e.g. twice daily for 30 min in rats) (Routtenberg, 1968; Kanarek and Collier, 1983). One of the measures of increased running wheel activity (RWA) in the ABA model is the increase of activity in the hours preceding the period of food availability (Mistlberger, 1994; Richter, 1922). This phenomenon, known as food-anticipatory activity, is considered an equivalent to the search for food.

Binge models

Several animal models of binge eating have been developed, each of which addresses certain aspects of the disorder. Three models will be discussed with their pharmacological interventions.

The stress-induced hyperphagia model

This model evokes hyperphagia of palatable food as a result of alternating exposure to periods of food restriction and unlimited food access in combination with acute stress (Hagan *et al.*, 2002; 2003; Artiga *et al.*, 2007). The stress-induced hyperphagia model has been proposed to model the occurrence of binge eating because of negative emotional states and stress. Consistently, administration of a corticotropin-releasing factor CRF_1 receptor antagonist resulted in an attenuation of stress-induced palatable food intake (Avena, 2013).

The sham-feeding model

This model aims to simulate the disturbances in satiety observed in BN patients (Davis and Campbell, 1973). Meals consisting of liquid food ingested by rats increase dramatically because of the draining of consumed food using a stomach cannula. Defective satiation caused by the cannula results in increased meal size. As a consequence, with time, rats learn to eat even more. This model is considered the most suitable of all available BN models to simultaneously mimic overeating, postprandial vomiting and impaired satiety (Casper *et al.*, 2008).

Limited-access model

In this model, non-food-deprived rats develop binge-like behaviours after having limited access to an optional palatable fatty and/or sugary food (Corwin and Wojnicki, 2006; Wojnicki *et al.*, 2007). Administration of 2-hydroxyestradiol, an estrogen metabolite, resulted in increased bingeing behaviour (Babbs *et al.*, 2011; 2013). These results were especially driven by effects on male rats, while subtle effects were observed in female rats. This might be a novel mechanism for the sex differences in the risk of developing eating disorders.

Processes underlying eating disorders

Food intake and energy expenditure consisting of resting metabolism, physical activity and the thermogenic effect of food need to be in balance to maintain a stable and normal body weight. In eating disorders, this balance is shifted by an excessive or restricted food intake. Food intake is influenced by hunger, satiety and pleasure, which are regulated by a number of brain areas and neurotransmitters. Central biogenic amine systems that use dopamine, noradrenaline or 5-HT (serotonin) as neurotransmitters regulate many aspects of energy balance, such as feeding, motor activity, maintenance of body weight, mood, impulsivity and anxiety. Lesioning and electrical stimulation studies have indicated that separate, partly overlapping, neural circuits of the hypothalamus and brainstem regulate meal initiation and termination respectively (Hetherington and Ranson, 1940; Brobeck *et al.*, 1943; Anand and Brobeck, 1951; Hoebel and Teitelbaum, 1966; Herberg and Blundell, 1967; Thomas and Mayer, 1968; Olney, 1969; Leibowitz *et al.*, 1981; Seeley *et al.*, 1994; Choi and Dallman, 1999).

Besides regulation by homeostatic processes, neuronal circuits involved in the reinforcing effects of reward also influence food intake. The nucleus accumbens, with connections to the amygdala, the lateral hypothalamus (LHA) and the ventral tegmental area, has been implicated in the hedonic control of energy consumption (Hernandez and Hoebel, 1988; Mendoza *et al.*, 2005). In the next chapters, we first describe the general role of a neurotransmitter in feeding and then address its role in models of eating disorders. The effects of dopamine, 5-HT and noradrenaline transmission on feeding are summarized in Table 1.

Dopaminergic modulation of feeding

Dopamine is a neurotransmitter with a crucial role in eliciting reward-related behaviour, arousal, cognition and locomotor activity. This transmitter also plays a pivotal role in feeding behaviour and produces different actions at different brain regions, most importantly in striatal and hypothalamic nuclei. Striatal dopamine regulates food preference and the reinforcing effects of food, such that eating induces dopamine release in striatum, which correlates with palatability and rewarding aspects of the meal (Small *et al.*, 2003; Cooper and Al-Naser, 2006).

Hypothalamic dopamine is required to initiate each meal and its release influences both meal duration and meal number (Meguid *et al.*, 2000). The effects of hypothalamic dopamine depend on the actions of dopamine on selected nuclei and dopamine receptor subtypes, overall metabolic status and the route of administration of dopamine modulating signals (Ramos *et al.*, 2005). The dopaminergic neurons from the ventral tegmental area and the substantia nigra to the hypothalamus influence feeding behaviour by dual action (Wellman, 2005). First, both transient and constant pharmacological increases of dopamine in the LHA decrease food intake (Vucetic and Reyes, 2010). Dopamine in the LHA increases in response to feeding, remains elevated during meal consumption, initiates meal termination by reaching a

Table 1

The effects of different neurotransmitters during feeding

Neurotransmitter	Brain region	Change in neurotransmitter during meal consumption	Effect on meal size and food intake	Mechanism
Dopamine	Striatum	Increased	Reduced	Reward and reinforcement
	Lateral hypothalamus	Increased	Reduced	Regulation of meal size via initiation of meal termination
	Ventromedial hypothalamus	Decreased	Reduced	Regulation of meal size and compensatory change in meal frequency
5-HT (serotonin)	Hypothalamus	Increased	Reduced	Satiety and satiation
	Nucleus accumbens	Increased	Reduced	Motivation to eat
Noradrenaline	Anterior hypothalamus/ paraventricular nucleus	Increased	Activation of α_1- or β_2-adrenoceptors enhances food intake; activation of α_2-adrenoceptors reduces meal size and food intake	Satiety

'threshold' level and again normalizes after meal termination (Meguid *et al.*, 2000). Meal size positively correlates with the amount of dopamine released in the LHA (Meguid *et al.*, 1995). Further supporting the role of LHA dopamine in AN, a dopamine D_2 receptor antagonist given into the LHA counteracted amphetamine-induced AN (Gilbert and Cooper, 1985).

Second, dopamine in the hypothalamic ventromedial nucleus (VMN) decreases meal size and food intake (Vucetic and Reyes, 2010). The dopamine levels in the VMN decrease during eating and return to baseline during fasting, such that a rat starts a new meal when food is again available (Meguid *et al.*, 1997). Degree and duration of reduced dopamine levels in the VMN positively correlate with meal size and particularly with a compensatory decrease in meal frequency (intermeal interval) that is meal number (Meguid *et al.*, 2000). Shortly, the net effect of dopamine on feeding is determined by changes in synaptic dopamine levels of striatal and hypothalamic nuclei, which vary during feeding and fasting (meal – interval) and depend upon brain region (Table 1).

Bridging AN to its animal models with dopamine

There is neurotransmitter, neuroimaging and genetic evidence that dopamine is altered in AN and reduced dopamine metabolism relates to the state of low weight. The levels of the dopamine metabolite, homovanillic acid (HVA), in CSF were reported to be reduced in AN (Gillberg, 1983; Barbarich *et al.*, 2003). After weight recovery, the abnormal levels of HVA in CSF seem to normalize (Kaye *et al.*, 1984).

Women who had recovered from AN did not seem to distinguish between positive (rewarding) and negative (anhe-

donic) events, shown by their responses in the anterior ventral striatum, an area strongly influenced by dopamine transmission (Wagner *et al.*, 2007). On the other hand, activation in the ventral striatum was higher in AN during processing of underweight stimuli than when processing normal-weight stimuli, while the opposite was observed in healthy controls (Fladung *et al.*, 2010). The AN patients may thus be able to experience reward and pleasure, but their appreciation of rewarding stimuli may be altered. Self-starvation may be driven by inappropriately assigned pleasure associated with food restriction through the ventral striatal dopamine reward system.

Women who recovered from AN showed higher D_2/D_3 receptor binding potential in the anteroventral striatum than controls and this positively correlated to harm avoidance in the dorsal caudate and dorsal putamen (Frank and Kaye, 2005; Frank *et al.*, 2005). The genes for D_2 and D_4, but not D_3 dopamine receptors were associated with AN, while findings from the dopamine-metabolizing enzyme, catecholamine-O-methyltransferase, gene were less conclusive (Rask-Andersen *et al.*, 2010). Another study found up-regulation of the dopamine transporter (DAT) and down-regulation of D_2 receptors in AN, but no association between D_4 receptors and AN (Frieling *et al.*, 2010). Thus, dopamine binding and genetic studies support an involvement of the dopaminergic system in AN.

Consistent with the individuals with AN, in the mouse ABA model, alterations in dopamine signalling have been linked to susceptibility to ABA. The A/J mice, that are more vulnerable to ABA than the C57BL/6J mice, show increased RWA, but lack food-anticipatory activity and motivation to eat when exposed to the ABA model (Gelegen *et al.*, 2008). These were accompanied by increased D_2 receptor expression in the caudate putamen. In ABA rats, dopamine release in the ventral striatum was normally increased during feeding

behaviour, but not during the initiation of food-anticipatory behaviour (Verhagen *et al.*, 2009). Treatment with cis-flupenthixol, a non-selective dopamine receptor antagonist, resulted in an attenuated body weight loss and increased food intake in ABA rats (Verhagen *et al.*, 2009). After blocking dopamine receptors with pimozide in ABA rats, light phase activity decreased and survival increased (Lambert and Porter, 1992). Animal data support decreased synaptic dopamine or increased D_2 receptor density in the ABA model, similar to those in the AN model. These changes may contribute to the characteristic harm avoidance, increased physical activity and disturbance of reward mechanisms contributing to anhedonia of feeding in AN.

Bridging binge eating to its animal models with dopamine

Like drug addiction, food overconsumption is characterized by lack of control over initiation and termination of consumption, compulsive behaviour, adaptation/sensitization to rewarding stimulus and inappropriate functioning of the brain dopamine reward system (Wang *et al.*, 2004). Palatable food, such as sugar and fat, increase dopamine levels in the nucleus accumbens (Hoebel *et al.*, 1989). Bulimic patients with a history of binge eating have lower levels of the dopamine metabolite HVA in CSF (Jimerson *et al.*, 1992), suggesting overeating as a compensatory response to the hypofunctional striatal dopamine signalling.

Down-regulation of D_2-type receptors and an attenuated response of striatal dopamine to (palatable) food and food cues are also associated with overweight (Volkow *et al.*, 2002; Stice *et al.*, 2010). Body mass index (BMI) and altered food intake because of attenuated dopamine signalling correlate with polymorphisms of the dopamine receptor genes DRD2, DRD4 and the dopamine-metabolizing enzyme MAO-A (Fuemmeler *et al.*, 2008; Kaplan *et al.*, 2008; Stice *et al.*, 2008; 2010). An epistatic interaction between catecholamine-O-methyltransferase and DAT1 genes on eating psychopathology and BED was reported (Hersrud and Stoltenberg, 2009). Obese individuals with BED overrepresent alleles in two genes, DRD2 and the μ-opioid receptor, as compared with other obese patients without BED (Davis *et al.*, 2009). Adaptations within the natural reward pathways, specifically the endogenous opioids and dopamine, have been implicated in the transition from overeating to (hedonic) binge eating (Mathes *et al.*, 2009). Thus, there is genetic evidence for an involvement of both opioid and dopamine signalling in the susceptibility to develop BED.

Prolonged binge-like intake of sugar increases dopamine release and D_1 receptor binding in the nucleus accumbens and reduces D_2 receptor binding in striatum in rats (Colantuoni *et al.*, 2001; Rada *et al.*, 2005). After 36 h of deprivation from sugar and chow, these rats display anxiety and reduced accumbal dopamine release as compared with rats that had not binge eaten the sugar (Avena *et al.*, 2008). The D_2 receptor down-regulation and D_1 receptor up-regulation in the VMN and down-regulation of D_1 receptors in the LHA were related to behavioural sensitization for having larger but less frequent meals (Fetissov *et al.*, 2002). Supporting the role

for altered dopaminergic activity in consumption of larger meals, rodent obesity models, genetic or environmental, display brain region specific changes in basal dopamine levels and D_2 receptor and DAT expression, as compared with lean animals (Figlewicz *et al.*, 1998; Fetissov *et al.*, 2002). Dopamine release in the LHA during eating is greater in obese than in lean rats, resulting in larger meal size (Yang and Meguid, 1995). In a sham-feeding model of bulimia, a D_2 receptor agonist failed to reduce sham feeding of 5% sucrose in gastric fistulated rats, but reduced it in intact animals, suggesting an ingestive response to D_2 receptor activation only when potent satiety stimuli are present (Cooper *et al.*, 1989). Opiate receptor antagonist naloxone was shown to attenuate sham feeding of sucrose solution in gastric fistulated rats and the μ-opioid receptor agonist DAMGO, stimulated high-fat consumption, supporting the role of opioid and dopaminergic reward pathways in overeating disorders and their animal models (Rockwood and Reid, 1982; Kirkham and Cooper, 1988; Will *et al.*, 2006).

Dopamine also interacts with several neuropeptides in the regulation of food intake (see Vucetic and Reyes, 2010) and these neuropeptides may open new ways to treat AN and are thus important to shortly mention. Melanocortin receptor activation results in decreased food intake, increased energy expenditure and stimulation of hypothalamic-pituitary-adrenal axis (reviewed by Hillebrand *et al.*, 2002). As these symptoms are also observed in ABA, a hyperactive melanocortin system might underlie ABA. Indeed, melanocortin binding sites are increased in the VMN during ABA (Kas *et al.*, 2003). Inhibition of the melanocortin pathway by chronic intracerebroventricular infusion of agouti-related protein(83-132) increased survival in ABA rats by increasing food intake, reducing physical activity and normalizing body temperature (Kas *et al.*, 2003). Stimulation of melanocortinergic activity by chronic intracerebroventricular infusion of α-melanocyte stimulating hormone was found to enhance ABA (Hillebrand *et al.*, 2005b). An increased RWA during the light phase decreased food intake and body weight and increased activity of the hypothalamic-pituitary-adrenal axis were observed. Conversely, treatment with neuropeptide Y in ABA rats increased running and decreased food intake (Nergårdh *et al.*, 2007).

Leptin has been shown to reduce hyperactivity in rats exposed to the SIH model. Both pro-opiomelanocortin neurons and neuropeptide Y/agouti-related protein neurons are sensitive to leptin. Stimulation of these neurons by leptin decreased food intake (Schwartz *et al.*, 1997; Friedman and Halaas, 1998; Cowley *et al.*, 2001). Weight loss is further promoted by leptin as it also exhibits metabolic effects, for example increased energy expenditure and thermogenesis (van Dijk, 2001). Chronic intracerebroventricular administration of leptin decreased RWA and food intake and increased energy expenditure by thermogenesis in rats during exposure to the ABA model (Hillebrand *et al.*, 2005c). This reduction in hyperactivity by leptin administration could not offset the decline in food intake and the increased thermogenesis, resulting in weight loss and increased mortality.

Another hormone of interest in the pathophysiology of AN that interacts with dopamine is ghrelin. Ghrelin GHS-R1a receptors in the ventromedial hypothalamus (VMH) and dorsomedial hypothalamus were shown to mediate

food-anticipatory activity (Merkestein *et al.*, 2013). A diminished food-anticipatory activity and unaltered food intake were observed after administration of a ghrelin receptor antagonist by an acute intracerebroventricular injection in rats or by chronic peripheral administration in mice (Verhagen *et al.*, 2011).

Besides the leptin-melanocortin pathway, the potential role of reward pathways and the endocannabinoid system in AN has become of research interest. Although treatment of ABA mice with a cannabinoid agonist, Δ^9-tetrahydrocannabinol (THC), or an endocannabinoid uptake inhibitor, OMDM-2, increased food intake, it was not sufficient to attenuate weight loss and treatment with the agonist even further decreased survival in ABA mice (Lewis and Brett, 2010). In rats, administration of THC did not result in an increased mortality rate, which might be explained by species differences. On the contrary, Verty *et al.* (2011) report increased food intake, reduced body weight loss and altered RWA following cannabinoid agonist administration in ABA rats (Verty *et al.*, 2011).

5-HT modulation of feeding

Brain microdialysis shows an increase in the release of 5-HT in the rat hypothalamus during eating and pre-ingestive events (Schwartz *et al.*, 1990). Hypothalamic 5-HT is involved in satiety and satiation processes and 5-HT release is increased following the ingestion of a meal to generate a satiety signal for the termination of the meal (Table 1) (Haleem, 1993b). Caudal 5-HT neurons control the excitability of the projection area of nucleus tractus solitarius, the parabrachial nucleus, and inhibit feeding likely via 5-HT$_3$ receptors in the nucleus tractus solitarius because blocking these receptors protects against starvation when agouti-related protein neurons are ablated (Wu *et al.*, 2012). Pharmacological agents that increase 5-HT neurotransmission by enhancing 5-HT release and inhibiting its reuptake, with d-fenfluramine (Gibson *et al.*, 1993), or by selectively inhibiting 5-HT reuptake, with fluoxetine (Tao *et al.*, 2002), reduce food intake in humans and experimental animals (Heisler *et al.*, 1999; Halford *et al.*, 2007). The inhibitory action of 5-HT agents on food intake is likely mediated via postsynaptic 5-HT$_{1B}$ and 5-HT$_{2C}$ receptors in the hypothalamus (Kennett and Curzon, 1988). In contrast, activation of 5-HT$_{1A}$ receptors stimulates feeding in normal-weight animals (Voigt *et al.*, 2002).

In addition to the hypothalamus, 5-HT influences food intake through the nucleus accumbens (Table 1). This brain area is involved in food-related reward, modulation of the physiological drive to eat and appetite-suppressant 5-HT signalling to the hypothalamus (Georgescu *et al.*, 2005). The nucleus accumbens contains a high density of 5-HT$_4$ receptors and pharmacological or genetic inhibition of 5-HT$_4$ receptors in mice reduced food intake in fed mice, but not in food-deprived mice (Jean *et al.*, 2007). Deletion of 5-HT$_4$ receptors also attenuated responses to stress- or ecstasy (MDMA)-induced hypophagia (Compan *et al.*, 2004; Jean *et al.*, 2007). These studies suggest a role of 5-HT$_4$ receptors in the inhibition of the drive to eat, which can particularly be seen in fed animals. Thus, 5-HT release in hypothalamus strongly regulates feeding by enhancing satiety and satiation,

while striatal 5-HT can modulate motivational aspects of food intake either directly or via interactions with for example, dopamine transmission (Table 1).

Bridging AN to its animal models with 5-HT

In addition to feeding, 5-HT has been associated with many behavioural changes in AN, such as refusal to eat, excessive exercise or hyperactivity, stress, depression/anxiety and impaired impulse control. Restricted feeding and malnutrition in AN reduce brain 5-HT content, the 5-HT metabolite 5-HIAA in CSF and tryptophan in plasma, but these return to normal after weight recovery (Schweiger *et al.*, 1986; Kaye *et al.*, 1988; Attia *et al.*, 2005). Indeed, the reduced availability of tryptophan, the precursor of 5-HT, because of restricted diet can reduce the 5-HT synthesis and neurotransmission (Haleem and Haider, 1996). The diet-induced reduction of tryptophan was associated with decreased anxiety in AN, suggesting restricting dietary intake may represent a mechanism to counteract dysphoric mood in AN (Kaye *et al.*, 2003).

Low 5-HT levels may be compensated by up-regulation of 5-HT$_{2C}$ receptor-mediated responses after food restriction (Cowen *et al.*, 1996). Moderate dieting in healthy women reduces plasma tryptophan, but increases the prolactin response to 5-HT releaser d-fenfluramine or to a 5-HT$_{2(C)}$ agonist meta-chlorophenylpiperazine, suggesting a functional sensitivity of 5-HT$_{2C}$ receptors after reduced brain 5-HT levels (Cowen *et al.*, 1996). One study suggested reduced 5-HT$_{2A}$ receptor binding in the mesial temporal lobe and in some other cortical regions in active and even recovered AN (Frank *et al.*, 2002).

Polymorphism of 5-HT$_{2A}$ receptor and 5-HT transporter (SERT; SLC6A4) genes may increase the risk for AN (Hinney *et al.*, 2010; Clarke *et al.*, 2012). Weight loss in teenage girls was linked to a polymorphism of 5-HT$_{2C}$ receptors (Westberg *et al.*, 2002). A meta-analysis suggested that the genetic variance of SERT-linked genes contributes towards the susceptibility to AN (Lee and Lin, 2010), while another study did not find an association between this genotype and recovery from AN (Castellini *et al.*, 2012).

Long-term dietary restriction (several days or weeks) reduces plasma tryptophan levels, brain synthesis and content of 5-HT and density of in rats (Haleem and Haider, 1996; Huether *et al.*, 1997). In ABA rats, the initiation of food-anticipatory behaviour failed to increase accumbal 5-HT release, the levels of 5-HT remained low and their circadian activity was blunted (Verhagen *et al.*, 2009). In spite of low 5-HT levels, rats starved for 4 days showed post-fasting anorexia, suggesting an up-regulation of satiety signals (Duhault *et al.*, 1993). The enhanced satiety and suppression of appetite may result from a compensatory up-regulation of 5-HT receptors that occurs after restricted diet-induced reduction of brain 5-HT content (Haleem and Haider, 1996). Similar to women on a diet, the prolactin response to meta-chlorophenylpiperazine was increased in rats after restricted diet, indicating a functional up-regulation of 5-HT$_{2C}$ receptors (Franklin *et al.*, 1999). However, prolactin responses to 5-HT$_{1A}$ or 5-HT$_{2A}$ agonists were small and only transient, suggesting

that only some, but not all, 5-HT receptor subtypes are up-regulated in response to low brain 5-HT (Franklin et al., 1999).

Dysregulation of 5-HT neurotransmission underlying behavioural changes in AN further supports the sex differences in AN. Central synthesis, metabolism and functional responses of 5-HT and the anorectic effect of 5-HT via the $5-HT_{2C}$ receptor (located on the X-chromosome) are greater in female than in male rats (Haleem, 1993a). The $5-HT_{1A}$ or $5-HT_{2C}$ receptor activation or exposure to stress increases corticosterone in plasma more in female rats than male rats (Haleem et al., 1989; Haleem, 1993a). There is thus evidence to support a role for 5-HT in pathophysiology of AN. However, considering that 5-HT regulates several different behaviours, it cannot be ruled out that the other behavioural changes, such as stress, may contribute to 5-HT dysregulation and anorexia.

Bridging binge eating to its animal models with 5-HT

Findings from 5-HT dysfunction in BN or BED are complex and often overlap with findings from obese humans or animals, such that the 5-HT dysfunction in the two conditions cannot be completely separated. Bulimic patients with a history of binge eating have reduced levels of 5-HT metabolite 5-HIAA in CSF and the 5-HIAA level inversely correlates with binge frequency (Jimerson et al., 1992). Low central 5-HT activity may contribute to blunted satiety responses in BN. Several 5-HT receptor subtypes, namely $5-HT_{1B}$, $5-HT_{2A}$, $5-HT_{2C}$, $5-HT_4$ and $5-HT_6$, are implicated in the pathophysiology of eating disorders. The $5-HT_{2A}$ receptor binding in the cerebral cortex positively correlates to BMI (Erritzoe et al., 2009) and $5-HT_{2A}$ receptor binding in the midbrain was still altered in patients who had recovered from BN, suggesting altered 5-HT function even after recovery from BN (Kaye et al., 2001). There is a strong positive association between BMI and cerebral SERT binding or $5-HT_4$ receptor density in the nucleus accumbens, ventral pallidum, left hippocampal region and orbitofrontal cortex (Erritzoe et al., 2010; Haahr et al., 2012). Obese binge-eating women have decreased SERT binding in the midbrain compared with obese controls (Kuikka et al., 2001). Up-regulation of $5-HT_{2A}$ receptors and down-regulation of SERT may be compensatory changes to lower brain 5-HT content in overweight individuals, leading to increased food intake (Erritzoe et al., 2009).

Changes in food intake and BMI correlate with polymorphism of $5-HT_{2A}$ receptors and SERT (Fuemmeler et al., 2008; Sorlí et al., 2008). These may not directly be genetic risk factors for eating disorder, but play a role in determining BMI in obese subjects (Sorlí et al., 2008; Munn-Chernoff et al., 2012). In spite of being implicated in obesity, polymorphism of the human $5-HT_{2C}$ receptor have not clearly been associated with BN or BED (Burnet et al., 1999; Nacmias et al., 1999).

Further evidence for the role of 5-HT in pathophysiology of BED originates from genetic and environmental animal models. The hypothalamic 5-HT release was decreased, SERT binding was lower and $5-HT_{2A}$ and $5-HT_4$ receptor binding

was higher, particularly in the reward-mediating nucleus accumbens shell in genetic or diet-induced obese rodents (De Fanti et al., 2000; Ratner et al., 2012). Chronic hyperphagia increased hypothalamic $5-HT_{2A}$, $5-HT_{2C}$ and $5-HT_{1B}$ gene expression, and on the contrary, inactivation of $5-HT_{2A}$ receptors inhibited overfeeding and obesity in A(y) mice expressing the ectopic agouti protein (Nonogaki et al., 2006a,b). Moreover, $5-HT_6$ and $5-HT_4$ receptors have been suggested to play a role in overeating and obesity. Mice carrying a non-functional $5-HT_6$ receptor consumed less high-fat diet, gained less weight and had less fat accumulation (Frassetto et al., 2008). The $5-HT_4$ receptor is involved in food intake and pharmacological or genetic manipulation of $5-HT_4$ receptor in reward-related brain areas alters food intake (Jean et al., 2007).

Noradrenergic modulation of feeding

From the locus coeruleus noradrenergic fibres innervate the neocortex, thalamus, amygdala, hippocampus, hypothalamus and spinal cord. Noradrenaline is released during consumption of a meal within the anterior hypothalamus, but not within the lateral ventricles (Martin and Myers, 1975). The increase in noradrenaline in the paraventricular nucleus correlates with the size of a meal: when rats consumed large meals under satiated conditions at dark onset, levels of noradrenaline were higher than when rats consumed small meals (Table 1) (Paez et al., 1993). Noradrenaline can either elicit food intake or promote satiety depending on the site of application (Table 1). Low local concentration of exogenous noradrenaline in the hypothalamic paraventricular nucleus, innervated by noradrenergic fibres, elicited vigorous feeding (Grossman, 1975). Application of noradrenaline into the rat perifornical hypothalamus reduced eating, possibly by promoting satiety via α-adrenoceptors (Margules, 1970). Lesions positioned within the ascending ventral noradrenergic tracts, the paraventricular nucleus, the lateral border of VMN or the more caudal regions can result in depletion of noradrenaline and overeating to obesity (Ahlskog and Hoebel, 1973; Kirchgessner and Sclafani, 1988).

α-Adrenoceptor subtypes within the paraventricular nucleus exert antagonistic actions on feeding. Stimulation of α_1- or β_2-adrenoceptors activates descending feeding-inhibitory fibres in the paraventricular nucleus, which suppresses food intake. Activation of α_2-adrenoceptors in the paraventricular nucleus induces inhibitory postsynaptic potentials, which results in disinhibition of the descending satiety cells, which, in turn, stimulates food intake (Wellman, 2000). Thus, pharmacological manipulations with direct adrenoceptor agonists or drugs that release noradrenaline or block transport of noradrenaline can increase or decrease food intake, depending on the site and type of noradrenaline manipulation. Many anti-obesity drugs, such as sibutramine and amphetamine, are suggested to reduce eating via release of noradrenaline and subsequent activation of α_1-adrenoceptors (Ahlskog and Hoebel, 1973; Janhunen et al., 2011).

The paraventricular nucleus exhibits a reliable rhythm in the secretion of endogenous noradrenaline over the dark and

light cycle. Microdialysis studies indicate that extracellular levels of noradrenaline within the paraventricular nucleus peak at the onset of the dark cycle, a period during which rats engage in eating (Figure 1) (Morien *et al.*, 1995). Sensitivity to the stimulatory action of noradrenaline on feeding is higher at the onset of the dark, which may relate to increased numbers of α_2-adrenoceptors within the paraventricular nucleus at the onset of dark (Jhanwar-Uniyal *et al.*, 1986). The effects of noradrenaline on feeding and meal size can thus vary from hypophagia to hyperphagia, depending upon the subset of adrenoceptors and the brain region activated (Table 1).

Bridging AN to its animal models with noradrenaline

Noradrenaline is involved in arousal, alertness, anxiety, stress, mood and it affects activity of the reward system. Central and peripheral noradrenergic pathways are down-regulated in prolonged fasting and acute AN (Halmi *et al.*, 1978). The noradrenaline levels in CSF are normal in under-weight and weight-restored AN patients, but lower in long-term weight-recovered patients (Kaye *et al.*, 1985), indicating a potential intrinsic disorder in central noradrenaline metabolism. Indeed, the noradrenaline response to a meal or exercise is reduced in AN patients (Pirke, 1996), but tends to normalize with weight gain and recovery (Kaye *et al.*, 1985; Pirke, 1996).

As noradrenaline plays a role in stress behaviours, it is possible that stress contributes to altered noradrenaline transmission and AN. Noradrenaline also plays a role in anxiety, an important symptom of AN, and genes encoding proteins which remove noradrenaline from the synapse are good candidates for affecting susceptibility to AN. Polymorphism of the noradrenaline transporter protein, NET (SL6A2) were associated with AN (Urwin *et al.*, 2002), however, another study did not confirm this association (Hu *et al.*, 2007). A polymorphism of the noradrenaline-metabolizing enzyme, MAO-A, may affect susceptibility to AN, particularly the restricting AN (Urwin *et al.*, 2003). MAO-A, NET and SERT gene variants appear to contribute additively to the risk of developing restricting AN (Urwin *et al.*, 2003; Urwin and Nunn, 2005).

In the ABA model, the hypothalamic noradrenaline turnover, estimated by the concentration of its major metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG, MOPEG), was decreased in male rats with restricted feeding, but hyperactivity compensated this reduction (Broocks *et al.*, 1990). Another study suggested that changes in food intake in ABA rats are due to increased activity of the hypothalamic-pituitary-adrenal axis rather than altered noradrenaline concentration (Burden *et al.*, 1993). Interestingly, reduced noradrenaline turnover could underlie hyperactivity in AN and ABA because NET-deficient animals show enhanced responses to locomotor stimulation and because running activity of the semistarved rats can be blocked by α_2-adrenoceptor agonists (Pirke *et al.*, 1993). In addition to AN and hyperactivity, the low noradrenaline neurotransmission could underlie symptoms, such as low blood pressure,

anxiety and mood disorder, found in AN patients. All in all, the role of noradrenaline in AN is complex and noradrenaline can contribute to several central and peripheral characteristics of AN.

Bridging binge eating to its animal models with noradrenaline

The noradrenergic system stimulates hunger and preferential consumption of carbohydrates in experimental animals and humans (Leibowitz, 1990; Paez *et al.*, 1993). Impaired central noradrenaline function has been found in AN (described earlier), major depressive disorder, obsessive compulsive disorder and panic disorder. These pathologies are often associated with, or possibly concurring in, the development of BN (Kaye, 2008). However, the question whether central noradrenaline function is altered in BN needs more investigation. In the symptomatic phases of BN, noradrenaline levels in CSF are lower than in healthy controls, but return to normal baseline during recovery (Kaye *et al.*, 1990a,b). Bingeing behaviour in BN was suggested to parallel with overactivity of hypothalamic α-adrenoceptors (Kaye and Weltzin, 1991). Basal levels of noradrenaline in plasma do not differ between BN and healthy individuals. A meal produces a higher increase of noradrenaline in BN, while the noradrenaline responses in plasma to pharmacological challenge with isoprenaline, exercise or stress are blunted compared with controls (George *et al.*, 1990; Brambilla, 2001). Intake of highly caloric diets increases peripheral turnover and plasma levels of noradrenaline, which likely contributes to increased excretion of noradrenaline and hypertension (Kotsis *et al.*, 2010).

There is a lack of evidence for the role of noradrenaline transmission in BN or BED in humans and animals. The few studies have investigated noradrenaline transmission in over-eating or obese individuals. The thalamus, a part of the motivational neurocircuitry, becomes activated during pictures of high- versus low-calorie foods (Killgore *et al.*, 2003). The NET binding potential was reduced in the thalamus in obese individuals (Li *et al.*, 2013). Food craving positively correlates with activation of the thalamus and cortical-limbic-striatal areas during cues of favourite food and stress in obese, but not lean individuals (Jastreboff *et al.*, 2013). Reduced NET activity in thalamic areas may underlie stress-induced over-eating and obesity.

There is no clear evidence whether and how noradrenaline and adrenoceptors are altered in animals modelling BN or BED. Reduced brain noradrenaline metabolism, particularly in the hypothalamic VMN, LHA, paraventricular and dorsomedial nucleus, has been reported in genetic or diet-induced obese rodents (Johnston *et al.*, 1986; Levin, 1995). Obese rats and mice exhibit increased number of α_2-adrenoceptors located specifically in the paraventricular nucleus and in controlling energy intake and expenditure, in relation to high-fat diet. Furthermore, they display differences in genetic and hormonal factors that are known to contribute to the onset and maintenance of obesity (Jhanwar-Uniyal *et al.*, 1988; 1991; Levin, 1996).

Treatment of AN with monoaminergic agents

Currently, the first line of treatment for underweight patients with AN, is feeding and weight restoration, combined with psychotherapy. In ABA rats, certain palatable diets have been found to affect the development of, and recovery from, ABA (Brown *et al.*, 2008). Evidence for the efficacy of drug treatments for AN is limited, and currently there are no FDA or EMA approved drugs for the treatment of AN.

As described earlier, there is considerable evidence that patients with AN and BN have disturbances in dopamine, 5-HT and noradrenaline neurotransmission. Dopamine receptor agonists, including levodopa, have not been found to produce positive effects on weight gain in AN (Johnson *et al.*, 1983). As antipsychotics affect dopamine, 5-HT and noradrenaline systems and affect feeding and body weight, it seems possible that they might also facilitate recovery from AN and BN. In the ABA animal model, the non-selective dopamine receptor antagonist, *cis*-flupenthixol, reduced activity levels, increased body weight and increased food intake (Verhagen *et al.*, 2009). The atypical antipsychotic olanzapine reduced wheel running, starvation-induced hypothermia and activation of the hypothalamus-pituitary-adrenal axis, and thereby diminished development of ABA in rats (Hillebrand *et al.*, 2005a). Olanzapine treatment also reduced physical activity in hyperactive AN patients in a subsequent small open-label study (Hillebrand *et al.*, 2005a). One-week treatment with olanzapine increased survival and reduced food-anticipatory activity in ABA mice, but it did not alter food intake or RWA during *ad libitum* feeding or restriction conditions, or in mice housed without wheels (Klenotich *et al.*, 2012). Possible sedative effects by high doses of olanzapine may have caused the different outcomes.

There are several case series reporting efficacy of antipsychotics in AN, including olanzapine, chlorpromazine, haloperidol, quetiapine and aripiprazole. Meta-analysis, however, failed to demonstrate efficacy for antipsychotics for body weight and related outcomes in females with AN (Kishi *et al.*, 2012). There are nine randomized, controlled trials with contradictory findings from the efficacy of antipsychotics in AN. Olanzapine, studied in five trials, showed superiority to placebo in three studies, to chlorpromazine in one study and to aripiprazole in one study in terms of weight gain and/or reduction in obsessional symptoms (see Brewerton, 2012). Pimozide, but not risperidone or sulpiride, tended to facilitate weight gain as compared with placebo. Quetiapine had no efficacy in AN in a double-blind placebo-controlled trial (Powers *et al.*, 2012). The use and efficacy of first-generation antipsychotics is often limited by adverse effects (Krüger and Kennedy, 2000). However, atypical antipsychotics, such as olanzapine, may be advantageous by reducing psychological symptoms that contribute to early relapse, including obsessions and depression.

The ABA rats treated with fenfluramine, a 5-HT releasing agent, prior to the daily 2 h food access displayed an accelerated rate of weight loss (Atchley and Eckel, 2005). However, another group reported only hypodipsia upon chronic treatment with fenfluramine in ABA rats, which may explain the loss of body weight (Hillebrand *et al.*, 2006). The discrepancy between these findings may result from differences in methodology, animal species and strain and oestrous cycle (Hillebrand *et al.*, 2006). Chronic administration of a selective 5-HT reuptake inhibitor (SSRI) has been shown to reduce ABA in rats by attenuation of weight loss (Altemus *et al.*, 1996), decreased running activity (Altemus *et al.*, 1996; Yokoyama *et al.*, 2007) and increased food intake (Altemus *et al.*, 1996). In ABA mice, 4-week treatment with the SSRI fluoxetine increased food intake and reduced food-anticipatory activity, but did not alter survival (Klenotich *et al.*, 2012). Indeed, SSRI or other antidepressant medication seem to have limited effects in treating AN or preventing relapse (Walsh *et al.*, 2006). The prevalence of non-responders (roughly one out of two) and the presence of a functional genetic polymorphism in the promotor region of the gene for SERT emphasize the potential utility of psychopharmacogenetics in prescribing SSRIs in the treatment of AN patients (Gorwood, 2004). Antidepressants might still treat the AN-associated anxiety and depression and are thus commonly described in AN.

Cyproheptadine is a 5-HT and histamine antagonist that was first observed to stimulate appetite in allergic patients, and some suggested it could stimulate appetite in the AN (Capasso *et al.*, 2009). Systemic α_2-adrenoceptor agonist clonidine increases feeding and wheel running but does not affect rate of weight loss in ABA rats (Rieg and Aravich, 1994). In AN patients, clonidine did not show advantages over placebo.

Treatment of binge eating disorder with monoaminergic agents

Monoaminergic drugs are so far the most widely and successfully used group of compounds in the treatment of overeating and obesity. The first major class was composed of amphetamine-like releasers of dopamine, 5-HT and noradrenaline, including phentermine and fenfluramine, alone and in combination. In spite of clear appetite suppressant and anorectic effects, their use was limited by adverse effects in cardiovascular system and the combination was withdrawn from clinical use in the late 90s (reviewed by Kintscher, 2012). These compounds were followed by the reuptake inhibitor of 5-HT and noradrenaline, sibutramine that reduced food intake by enhancing satiety and consequently reduced body weight. The satiety-enhancing effect of sibutramine is mainly mediated by α_{2B}- and α_1-adrenoceptors and 5-HT$_{1B}$ receptors (Janhunen *et al.*, 2011). However, sibutramine's clinical use was limited in 2010 after it was reported to cause cardiovascular adverse effects such as hypertension (Kintscher, 2012). There are open-label and randomized, double-blind, placebo-controlled studies reporting that sibutramine reduces binge episodes, body weight and depressive symptoms in obese patients with BED (Appolinario *et al.*, 2002; 2003; Milano *et al.*, 2005; Bauer *et al.*, 2006).

There is also evidence that selective reuptake inhibition of either noradrenaline or particularly 5-HT has therapeutic efficacy in BN and BED. Antidepressants, especially SSRIs, are modestly effective in reducing binge eating over the short

term in BN and BED and over the long term in BN (McElroy *et al.*, 2012). Fluoxetine (60 mg) in obese patients with BED reduced weight and the number of binge attacks (Shapiro *et al.*, 2007). Fluvoxamine and sertraline also appeared to reduce the frequency of eating, the quantity of food and the amounts of carbohydrates, as well as facilitate the induction satiety (Hay and Bacaltchuk, 2002). Case studies suggest that inhibitors of noradrenaline reuptake, such as reboxetine or desipramine, reduce binge episodes and depression in BN (El-Giamal *et al.*, 2000). Topiramate has consistently been shown to decrease binge eating in BED and BN, but adverse effects limit its use (McElroy *et al.*, 2012). In rodent models of obesity, topiramate reduced food intake and increased energy expenditure, resulting in reduced body weight (Richard *et al.*, 2000). Also, tricyclic antidepressants, MAO inhibitors, mianserin, trazodone and bupropion have been shown to reduce binge episodes in humans (Bacaltchuk and Hay, 2003).

Similar to humans, in the animal model in which rats were submitted to caloric restriction and stress, sibutramine and fluoxetine inhibited (palatable) food intake in all conditions, topiramate selectively inhibited compulsive intake of highly palatable food and midazolam increased it, suggesting predictive validity for this preclinical model (Cifani *et al.*, 2009; Avena, 2013).

The dopamine and noradrenaline reuptake inhibitor, bupropion, decreased food consumption by reducing meal size, postponing meal initiation and increased locomotor activity in rats (Zarrindast and Hosseini-Nia, 1988; Janhunen *et al.*, 2013). Both effects likely contribute to bupropion's weight reducing properties in obese individuals (Gadde *et al.*, 2001). The effects of bupropion on meal size seem to be mediated via α_1- and α_{2B}-adrenoceptors and several dopamine receptor subtypes (Janhunen *et al.*, 2013).

Concluding remarks

Eating disorders, such as AN, BN and binge eating disorder, display complex underlying mechanisms, which emphasize the importance of predictive and translational animal models in understanding these disorders and their treatment. This review discusses the most widely used and representative animal models of eating disorders and the related changes in monoaminergic neurotransmitters. Dopamine, 5-HT and noradrenaline in hypothalamic and striatal regions regulate food intake, satiety and rewarding and motivational aspects of feeding. Reduced neurotransmission in these systems has been implicated in the pathophysiology of different eating disorders in humans. Consistently, several monoaminergic drugs have been found efficacious in animal models and some of them have proven useful in the treatment of eating disorders, particularly those with overeating symptoms in humans.

Acknowledgements

Conflict of interest

SKJ is employed by Orion Pharma, which sells one or more of the drugs mentioned in this review.

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