PHILOSOPHICAL TRANSACTIONS B

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Review

Cite this article: Moore CF, Panciera JI, Sabino V, Cottone P. 2018 Neuropharmacology of compulsive eating. *Phil. Trans. R. Soc. B* **373**: 20170024.
http://dx.doi.org/10.1098/rstb.2017.0024

Accepted: 4 August 2017

One contribution of 16 to a discussion meeting issue 'Of mice and mental health: facilitating dialogue between basic and clinical neuroscientists'.

Subject Areas:
neuroscience, behaviour

Keywords:
compulsive, addiction, eating, habit, withdrawal, inhibitory control

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THE ROYAL SOCIETY PUBLISHING

Neuropharmacology of compulsive eating

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Compulsive eating behaviour is a transdiagnostic construct observed in certain forms of obesity and eating disorders, as well as in the proposed construct of 'food addiction'. Compulsive eating can be conceptualized as comprising three elements: (i) habitual overeating, (ii) overeating to relieve a negative emotional state, and (iii) overeating despite adverse consequences. Neurobiological processes that include maladaptive habit formation, the emergence of a negative affect, and dysfunctions in inhibitory control are thought to drive the development and persistence of compulsive eating behaviour. These complex psychobehavioural processes are under the control of various neuropharmacological systems. Here, we describe the current evidence implicating these systems in compulsive eating behaviour, and contextualize them within the three elements. A better understanding of the neuropharmacological substrates of compulsive eating behaviour has the potential to significantly advance the pharmacotherapy for feeding-related pathologies.

This article is part of a discussion meeting issue 'Of mice and mental health: facilitating dialogue between basic and clinical neuroscientists'.

1. Introduction

Compulsivity is defined as a strong, irresistible internal drive to perform an action, typically contrary to one's will [1]. Within the context of feeding, compulsive eating behaviour has been considered as an underlying transdiagnostic construct of certain forms of obesity and eating disorders, as well as food addiction [2–4]. Obesity is defined as a body mass index (BMI) greater than or equal to 30 kg m^{-2} [5], and it is often a consequence of recurrent overeating [6]. Binge-eating disorder (BED) is defined by abnormal and excessive eating behaviours in distinct rapid episodes, many including the intake of palatable food (i.e. food high in fat and/or sugar) [7]. Recently, attention has been brought to the proposed construct of food addiction, which arises from the concept that certain foods may have addictive potential, and that overeating may in some cases represent an addicted behaviour [8]. Food addiction is diagnosed through the Yale Food Addiction Scale (YFAS), which uses criteria of Substance Use Disorders from the Diagnostic and Statistical Manual of Mental Disorders (DSM) modified to reflect addictive behaviours towards food [7–9], though it is important to note that this concept is not yet recognized as an official disorder in the DSM. Obesity, BED and food addiction are highly comorbid as, for instance, 40–70% of individuals with BED are obese [10,11], and the incidence of food addiction is estimated to be approximately 25% in obese individuals [12,13]. Thus, it is of key importance to understand the neuropharmacological mechanisms that underlie potential transdiagnostic constructs, such as compulsive eating behaviour, in order to identify potential shared therapeutic targets.

We recently conceptualized three key, and not mutually exclusive, elements describing compulsive eating behaviour: (i) habitual overeating, (ii) overeating to relieve a negative emotional state, and (iii) overeating despite adverse consequences [2]. In this review, we seek to examine the current understanding of the

multiple neuropharmacological systems underlying the three elements of compulsive eating behaviour. For the purpose of this review, we are discussing only evidence from animal models that do not involve either food deprivation or restriction unless otherwise noted, in the hope of a more reliable translation of the observed neuropharmacology of compulsive eating behaviour.

2. Psychobehavioural processes and neurocircuitry underlying the elements of compulsive eating behaviour

The three elements of compulsive eating behaviour can be broadly mapped to dysfunctions of three key brain regions involving reward learning, emotional processing and inhibitory control [2]. The first element, habitual overeating, refers to the process by which a once goal-directed behaviour becomes a maladaptive, stimulus-driven habit [14]. The basal ganglia, the main sites of associative learning, include the ventral striatum (or nucleus accumbens, NAc), known for its role in reward and reinforcement, and the dorsal components of the striatum (e.g. dorsolateral striatum, DLS), which are considered the site of habit formation [14]. Similar to what has been hypothesized for drugs of abuse, chronic, repeated stimulations of dopaminergic system in the NAc by palatable food and associated cues shifts signalling to dorso-striatal dopaminergic pathways resulting in habit formation [15]. Therefore, compulsive eating is thought to reflect a maladaptive stimulus-driven habit, which overrides voluntary, goal-directed actions.

The second element, overeating to relieve a negative emotional state, is defined as performing a behaviour (intake of palatable food) in order to alleviate a negative emotional state [16,17]. This element has historical roots in the symptoms related to obsessive compulsive disorder (OCD), and may involve engagement in compulsive behaviours to prevent distress, anxiety or stress prior to engagement or provide relief from distress, anxiety or stress during and following engagement of the behaviour [7,18,19]. The neurobiological processes underlying this element are twofold: within-system neuroadaptations producing functional desensitization of the mesocorticolimbic dopaminergic system, and between-system neuroadaptations that include the recruitment of the brain stress systems in the extended amygdala [20]. Thus, a withdrawal-induced negative emotional state encompasses decreased reward, loss of motivation for ordinary rewards [17] and increased anxiety [20]. Accordingly, the transition to compulsive eating is hypothesized to result from the food acquiring negatively reinforcing properties (i.e. overeating alleviating a negative emotional state) [17,20–22]. Importantly, withdrawal in this context is distinct from more traditional definitions of drug withdrawal (i.e. purely physical symptoms of dependence), and it rather refers to a motivational withdrawal syndrome characterized by dysphoria, anxiety and irritability when the reward sought is not available [2,16].

The third element, *overeating despite adverse consequences*, describes the loss of executive control over food intake observed as a continuation of maladaptive overeating in the face of the resulting physical, psychological and social negative consequences, where behaviour would typically be suppressed [23–25]. 'Loss of control' is proposed to reflect deficits in inhibitory control mechanisms intended to suppress inappropriate actions. Inhibitory control processes are subserved by two main systems within the prefrontal cortex (PFC), conceptualized as a 'GO' system (dorsolateral PFC (dlPFC), anterior cingulate (ACC) and orbitofrontal (OFC) cortices) and a 'STOP' system (ventromedial PFC, vmPFC). Hyperactivity of the GO system and hypoactivity of the STOP system are thought to underlie the loss of control characteristic of compulsive overeating despite consequences [26].

3. Neuropharmacological systems underlying the elements of compulsive eating behaviour

(a) Dopamine system

The mesocorticolimbic dopaminergic pathway plays a major role in motivated behaviour, and its dysfunction is hypothesized to contribute to all three elements of compulsive eating: habitual overeating, overeating to relieve a negative emotional state and overeating despite adverse consequences. In reinforcement learning, habit formation requires dopaminergic signalling in the anterior DLS [27]. Dopamine type-1 receptor (D1R) neurons, which make up the direct, striatonigral pathway, drive enhanced dendritic excitability [28], and its relative dominance compared to dopamine type-2 receptor (D2R) signalling is one hypothesized mechanism of accelerated habit formation by drugs of abuse and palatable food [29,30]. Animals with a history of intermittent access to palatable food show habitual eating behaviour, whereas chow-fed controls retain goal-directed food responding after devaluation [29]. In the DLS, animals that habitually overeat have increased c-fos activation in non-D2R–containing neurons, suggesting that D1R neurons are activated in habitual eating [29]. Furthermore, injections of SCH-23390, a D1R antagonist, into the DLS block the acquired habitual eating [29] and restore the sensitivity to devaluation in animals with a history of palatable food access.

Over time, overstimulation of the mesocorticolimbic dopaminergic system from chronic exposure to highly rewarding, palatable food is hypothesized to result in desensitization/downregulation, contributing to the emergence of anhedonia and motivational deficits [16,21]. Compulsive eating would therefore emerge as a form of paradoxical self-medication to relieve these symptoms. There is some evidence of downregulated dopamine signalling in obese individuals, as availability of striatal D2Rs [31–33] and blunted striatal responses to palatable food [34] have been found to be inversely correlated with BMI. Similarly, rats bred to be obesity-prone displayed decreased reward system functioning prior to [35] and following the development of obesity [36]. Following prolonged access to a high-fat diet, obese rats also exhibited compulsive eating behaviour and decreased striatal D2Rs [36]. Virally knocking down D2Rs within the striatum of rats prior to high-fat diet access worsened reward deficits and accelerated the emergence of compulsive eating behaviours [36], demonstrating a functional role of striatal D2Rs in compulsive eating. Thus, compromised dopamine signalling may cause overeating to compensate for such reward deficit. Lisdexamfetamine (LDX), a prodrug of *d*-Amphetamine, is the only pharmaceutical drug currently approved for treatment of BED, and works through modulation of monoamine transmission,

including dopamine. LDX has been shown to directly decrease compulsive eating in rats [37] as well as humans, as measured by the Yale–Brown obsessive compulsive scale modified for binge eating (Y–BOCS–BE) [38]. LDX administration produces sustained increases in striatal dopamine in rats [39], which could recover low dopaminergic states characteristic of compulsive overeating to relieve a negative emotional state.

Vulnerabilities or neuroadaptations of prefronto-cortical dopaminergic signalling are thought to underlie the loss of control that leads to continued intake despite negative consequences [4,40]. Within the PFC, specifically in the OFC and the ACC, the decreased dopamine activity seen in addiction and obesity is associated with decreased inhibitory control [41]. Lower striatal D2Rs, a consequence of obesity, are also associated with corresponding deficits in prefrontal activity [32,42]. Additionally, probably by increasing extracellular concentrations of dopamine in the PFC [39,43], LDX improved dysfunctions in inhibitory control in humans with BED [38] that are associated with overeating despite consequences. Thus, by increasing extracellular dopamine levels in the basal ganglia as well as prefrontal areas, LDX may effectively restore dopaminergic dysfunctions associated with both the second and third elements of compulsive eating.

(b) Opioid system

The mu- and the kappa-opioid receptor subtypes have been implicated in compulsive eating behaviour in varying degrees. The mu-opioid system is known traditionally for its role in hedonic feeding, though more recently has gained attention as a regulator of incentive motivation for food rewards and associated cues [44–46], key contributors to changes in action–outcome versus stimulus-driven, habitual overeating [47]. In humans with BED, the selective mu-opioid receptor antagonist GSK1521498 decreased consumption of palatable food as well as attentional bias to palatable food cues [48,49]. Naltrexone, a mixed opioid receptor antagonist, decreased neural responses to food cues in healthy subjects, as shown by a reduced activation of the ACC and the dorsal striatum [50]. Randomized controlled trials assessing naltrexone have shown mixed effects on binge eating [51]. A combination of naltrexone and bupropion, a norepinephrine–dopamine reuptake inhibitor, has been one of the most successful approaches [52,53], suggesting possible benefits of combination pharmacotherapy targeting multiple neurotransmitter pathways over a traditional single medication.

Changes in mu-opioid receptor systems also occur during withdrawal from palatable food, and they may play a role in the emergence of the negative emotional state that drives compulsive eating behaviour. Rats given intermittent sucrose access show upregulated mu-opioid receptor binding and downregulated enkephalin mRNA in the NAc, which is interpreted to reflect a compensatory mechanism to prolonged endogenous opioid release following palatable food overconsumption [54]. Consequently, a withdrawal state can be precipitated in these rats through administration of the mu-opioid antagonist, naloxone, resulting in somatic signs and anxiety-like behaviour [55]. Naloxone treatment was also shown to cause a drop in extracellular dopamine (−18 to 27%) and increased acetylcholine release (+15 to 34%) in sucrose-withdrawn rats relative to chow-fed controls [55].

There is also evidence for both mu- and kappa- opioid system dysfunction in the PFC in compulsive eating, hypothesized to underlie deficits in inhibitory control processes underlying overeating despite negative consequences. Mu-opioid receptor stimulation in the vmPFC was shown to both promote feeding [56] and induce deficits in inhibitory control [57], which resulted from increased motivational food value and disinhibited behavioural output [58]. Furthermore, within the medial PFC (mPFC), administration of naltrexone dose-dependently and selectively reduced consumption of, and motivation for, palatable food in an animal model of compulsive eating [59,60]. Conversely, naltrexone microinfusion into the NAc non-selectively suppressed chow and palatable food intake and motivation for food [60], demonstrating a selectivity of manipulations to prefrontal opioid signalling (versus striatal) on binge eating of palatable food. Furthermore, animals with intermittent access to a palatable diet displayed increased expression of the gene coding for the opioid peptide pro-dynorphin (PDyn) and reduced expression of the pro-enkephalin (PEnk) gene in the mPFC. These results suggest that neuroadaptations to the prefrontal opioid system contribute to maladaptive food intake, probably through dysfunction of inhibitory control processes [56].

(c) Corticotropin-releasing factor (CRF)-CRF1 receptor system

There is compelling evidence that the extra-hypothalamic corticotropin-releasing factor (CRF)–CRF1 receptor system is a driving factor of compulsive overeating to relieve a negative emotional state [20,61]. Chronic, intermittent cycles of palatable food exposure and withdrawal are hypothesized to progressively recruit the CRF–CRF1 receptor system [20], observed as an increase in CRF in the central nucleus of the amygdala (CeA) of animals during withdrawal from palatable food [20,62]. Upregulation of CRF–CRF1 system is hypothesized to ultimately produce the negative emotional state observed in withdrawal referred to as the 'dark side' of addiction [17,20,61]. Rats with a history of intermittent palatable food displayed anxiety- and depression-like behaviours when the palatable food was no longer available (i.e. withdrawal) [20,21,63,64]. Renewed access then resulted in overconsumption of palatable food and a complete alleviation of the negative emotional state [21]. Accordingly, administration of the selective CRF1 receptor antagonist R121919 into the CeA blocked both withdrawal-induced anxiety-like behaviour and compulsive eating of palatable food when access to the palatable diet was restored [20,61].

The CRF–CRF1 system in the bed nucleus of the stria terminals (BNST) may also underlie binge eating that is precipitated by stress in a binge model with a history of food restriction [65]. The BNST is involved in the stress response, and is activated by intermittent access to palatable food in an animal model that also uses cycles of stress [65]. R121919 infusion into the BNST was able to block stress-induced binge eating; developed through a history of food restriction [65]. In a different animal model of genetic susceptibility to stress-induced binge eating, stress increased brain expression of CRF mRNA in the BNST of binge-eating–prone, but not binge-eating–resistant rats [66]. Thus, CRF in the BNST may modulate compulsive eating driven by stressful conditions and may interplay with the CeA to cause negative emotional states.

Guided by promising evidence in animal models, in 2016, a randomized, double-blinded, placebo-controlled study analysed the effects of the CRF1 antagonist pexacerfont on stress-induced eating in healthy adult 'restrained eaters'. Although this study was terminated early for reasons unrelated to any adverse effects of pexacerfont, researchers found promising results in reductions in ratings of food problems/preoccupations using the YFAS, as well as reductions in food craving and eating, though independent of stress condition [67]. Even with reduced sample size, this clinical trial demonstrated a strong positive potential of CRF1 antagonists in reducing food cravings in chronic dieters, warranting future, fully powered studies [67]. CRF1 antagonists are proposed to be most effective in certain psychiatric disorders specifically demonstrating CRF overactivation; thus, future clinical trials evaluating efficacy of CRF1 antagonists specific to certain disorders, circumstances, or patient subgroups have been called for [68,69].

(d) Cannabinoid receptor 1 system

The cannabinoid receptor-1 (CB1) receptor system within the amygdala modulates the negative emotional state associated with compulsive eating. In drug addiction, repeated cycles of intoxication and withdrawal result in the recruitment of the endocannabinoid system within amygdalar circuits, which is hypothesized to act as a 'buffer system' to CRF–CRF1 receptor system overactivation [70,71]. Similarly, during withdrawal from palatable food, the endocannabinoid 2-arachidonoylglycerol (2-AG) and cannabinoid type 1 (CB1) receptor expression were found to be increased in the CeA [72]. Systemic and CeA site-specific infusion of the CB1 receptor inverse agonist rimonabant precipitated anxiety-like behaviour and anorexia of the standard chow diet during withdrawal from palatable food [72,73]. Importantly, rimonabant did not increase anxiety-like behaviour in chow-fed control animals [72,73]. Therefore, the endocannabinoid system of the amygdala is hypothesized to be recruited during withdrawal from palatable food as a compensatory mechanism to dampen anxiety. Thus, endocannabinoids may help buffer the negative emotional state associated with withdrawal from food, and rimonabant may precipitate a withdrawal-like syndrome in a subpopulation of obese individuals abstaining from palatable food as they attempt to lose weight (e.g. by dieting). This mechanism may therefore explain the emergence of severe psychiatric side-effects following rimonabant treatment in obese patients [74].

The CB1 system also contributes to overeating despite negative consequences. In rats with a history of intermittent access to palatable food, rimonabant decreased palatable food intake to a greater extent than in chow-fed controls and also blocked compulsive eating of palatable food in a light/dark conflict test [75]. While the exact site of action mediating this effect is unknown, rimonabant has been found to selectively increase catecholamines such as dopamine in the PFC [76], thus hypothetically restoring dysfunctions in inhibitory control processes associated with lower prefrontal dopamine signalling.

(e) Glutamatergic system

Two major classes of glutamatergic receptors (a-amino-3-hyrdoxy-5-methyl-4isoxazolepropionic acid (AMPA), and *N*-methyl-D aspartate (NMDA) receptors) have been found to be involved in to compulsive eating behaviours, specifically habitual overeating as well as overeating despite aversive consequences. Habitual intake of palatable food is dependent on AMPARs in the DLS, one of the main brain areas involved in habit formation. Infusion of the AMPA/kainate receptor antagonist, CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) into the DLS blocked habitual intake, restoring sensitivity to devaluation of the palatable food [29].

NMDARs are hypothesized to be associated with the element of overeating despite adverse consequences via an interaction with inhibitory control processes. Memantine, an NMDAR uncompetitive antagonist, reduced binge eating and 'disinhibition' of eating behaviours in an open-label, prospective trial with humans [77]. Memantine has also been shown to reduce impulsivity and enhanced cognitive control in compulsive shoppers [78], a proposed behavioural addiction with similarities to compulsive eating. In compulsive eating animals exposed to daily intermittent access to a palatable diet, microinfusion of memantine into the NAc shell reduced binge-like eating [23], indicating that the NMDAR system in the NAc shell is recruited in compulsive eating rats. Activity within the NAc is modulated by glutamatergic projections originating from the PFC [79–81]. Memantine also blocked food-seeking and compulsive eating of palatable food [23].

Within the NAc core, high-fat diet–induced obesity caused alterations in glutamatergic synaptic plasticity, including increased potentiation at glutamatergic synapses, loss in ability of these potentiated synapses to undergo long-term depression and slower NMDA-mediated currents [82]. Synaptic impairments were associated with food addictive-like behaviour, including increased motivation, excessive intake and increased food seeking when the food was not available [82]. Dysregulated signalling at cortico-accumbens synapses are hypothesized to impair normal accumbal processing of motivation information and inhibition of responding [83], probably resulting in loss of control over intake and overeating despite consequences.

(f) Sigma-1 receptor system

Sigma-1 receptors (Sig-1Rs) have been implicated in the pathophysiology of addictive disorders encompassing multiple drugs of abuse [84–90], and have also been shown to modulate compulsive overeating despite adverse consequences [59]. In animals with daily, intermittent access to palatable food, systemic treatment with the Sig-1R antagonist BD-1063 selectively decreased palatable food intake in a dose-dependent manner [59]. Additionally, in the same study, BD-1063 blocked compulsive eating behaviour in face of adverse conditions [59]. Bingeing, compulsive eating rats showed a twofold increase in Sig-1R protein levels in the ACC [59]. Thus, prefrontal Sig-1R system may play a role in compulsive eating [59], perhaps due to neuromodulation of dopamine and glutamate signalling [91,92].

(g) Cholinergic system

Imbalance in acetylcholine (ACh) signalling in the NAc is characteristic of withdrawal from drugs of abuse [93], and has also been observed during withdrawal from palatable food [55], implicating this system as a key player in the associated negative emotional state. Similarly, in rats with alternating access to sucrose solution and chow food, followed by 12 h with no food access to induce bingeing, both spontaneous and naloxone-precipitated withdrawal caused an

increase in extracellular ACh in the NAc [55,94]. This increased ACh was also accompanied by decreased dopaminergic signalling, as well as somatic withdrawal signs and anxiety-like behaviour [55]. Within the NAc, the functional interaction between dopaminergic and cholinergic systems has a critical effect on the motivation to eat [95,96], in that hungry rats stopped feeding if the balance between the two shifted towards cholinergic tone [97]. Elevated levels of ACh in the NAc also result in aversion during low dopamine states [96], and may therefore contribute to aversive state of withdrawal.

(h) Trace amine-associated receptor-1 system

Recent evidence suggests the trace amine-associated receptor-1 (TAAR1) system participates in compulsive overeating despite adverse consequences, probably through the involvement of PFC circuits. TAAR1 is a G-protein coupled receptor activated by trace amines as well as other neurotransmitters such as dopamine and serotonin [98]. The TAAR1 system has recently come under attention for evidence of its role in regulating the behavioural actions of psychostimulants [99] but also impulsive-like behaviour [100]. A recent study [101] explored the role of the TAAR1 system in binge and compulsive eating in rats following daily, intermittent access to palatable food. Systemic injections of the selective TAAR1 agonist RO5256390 fully and selectively blocked binge eating of palatable food, the expression of conditioned place preference for palatable food, as well as compulsive-like eating in a light/dark conflict test [101]. Furthermore, binge-eating animals had decreased protein expression of TAAR1 receptors in the PFC [101]. Injections of RO5256390 site specifically into the infralimbic, but not prelimbic, cortex recapitulated the blockade of bingeing in compulsive eating rats [101]. These results suggest that TAAR1 may have an inhibitory role over feeding behaviour, and that loss of this function may be responsible for compulsive binge eating. Interestingly, TAAR1s are also activated by amphetamine [98], the active metabolite in the BED therapeutic LDX [102]. LDX and TAAR1 agonism may, therefore, work through similar mechanisms to restore impaired prefrontal control over inhibitory behaviours.

(i) Serotonin system

Serotonin (5-hydroxytrptamine, 5-HT) neurotransmission has been extensively studied in feeding and eating disorders, including BED [103], and has been linked to compulsive behaviours in OCD and bulimia nervosa [104,105]. Patients with BED show reduced 5-HT release in the hypothalamus, lower 5-HT transporter binding in the midbrain, and higher 5-HT2a and 5-HT5 binding in the NAc shell [106–108]. Serotonergic drugs, such as selective serotonin reuptake inhibitors, have been studied as potential therapeutics for BED [109,110]. There is a known role for the serotonin system in anxiety and depressive disorders; and lower 5-HT activity was found to predict negative mood prior to binge eating [111]. One potential mechanism for 5-HT drugs to reduce binge eating was found to be through 5-HT2c receptor activation of dopamine neurons in the ventral tegmental area (VTA) [112]. The obesity medication lorcaserin (a 5HT-2c selective agonist) has been shown to reduce both homeostatic feeding as well as the incentive value of food through VTA 5-HT2c activation [113]. *d*-Amphetamine, which inhibits monoamine reuptake, including serotonin, has been shown to increase 5-HT concentrations in the striatum [114]. Thus, LDX may also restore serotonergic activity contributing to its ability to reduce compulsive eating behaviour.

(j) Orexin

The role of orexin (hypocretin) has a hypothesized role in addictive behaviours [115], including binge and compulsive eating, probably through modulation of palatable food reinforcement and palatable food–seeking behaviour [116]. An orexin-1 receptor (OX_1R) antagonist has been shown to selectively reduce binge eating of palatable food [117,118]. In addition, orexin neurons in the lateral hypothalamus are activated by food cues [119,120], and mediate both cue-induced potentiation of feeding [119] and cue-induced reinstatement of food-seeking behaviour [120]. Thus, orexin signalling directly modulates food-cue responsivity associated with habit formation, and may play a role in compulsive, habitual overeating.

There are known effects of the orexin system on depression and anxiety-like behaviour [121]; though this has not been extensively studied in the context of palatable food withdrawal. However, in animal models of binge eating that include a history of caloric restriction and/or stress found increases in orexin expression in the lateral hypothalamus [117,122]. It is hypothesized that caloric restriction and stress interact to reprogram orexigenic pathways and promote bingeing. Infusions of an OX_1R antagonist blocks binge eating in this model of restriction stress-induced binge eating [117]; demonstrating a hypothesized role in compulsive eating to relieve anxiety. However, it should be noted that restriction itself may cause neuroadaptations that promote compulsive eating [123,124] separate from a history of exposure to and bingeing on palatable food [23,59,64].

4. Discussion

The pathology underlying compulsive eating behaviours involves neuroadaptations in a variety of neurotransmitter and neuropeptide systems. There is much left to understand about the complexity of these behaviours and associated disorders, as well as disease process. The construct of compulsive eating has only recently gained attention, and debates over the definition of compulsive behaviour and its underlying psychobehavioural processes are actively ongoing. Thus, the present review focuses on the currently assumed neuropharmacological mechanisms that underlie the elements of compulsive eating, as it has been recently postulated by the authors [2]. Honing in on compulsive eating through increased research attention and dialogue among scientists will probably lead to evidence for additional systems involvement.

Complex disorders, such as obesity and eating disorders, require concerted efforts in preclinical and clinical research to relate neurobiological findings to behavioural indices (e.g. habits, anxiety states, inhibitory control), especially vital in studying obesity, an extremely heterogeneous disorder, where many studies have found conflicting neuropharmacological results [125]. Finally, identifying novel treatments that target one or more elements of compulsive eating behaviour specifically will have enormous therapeutic potential for millions of people with forms of obesity and/or eating disorders.

Data accessibility. This article has no additional data.

Authors' contributions. All authors made substantial contributions to conception and design of this review. C.M. and J.P. drafted the manuscript, and P.C. and V.S. substantially and critically revised it for intellectual content. All authors gave final approval for its submission

Competing interests. We declare we have no competing interests.

Funding. This work was supported by the National Institutes of Health (grant numbers DA030425 (P.C.), MH091945 (P.C.), MH093650 (V.S.), AA024439 (V.S.), AA025038 (V.S.) and DA044664 (C.M.)); the Peter Paul Career Development Professorship (P.C.); the McManus Charitable Trust (V.S.); and the Burroughs Wellcome Fund (C.M.) through the Transformative Training Program in Addiction Sciences [grant number 1011479]. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Acknowledgements. We are grateful to the Royal Society for their support of the costs of attending the meeting 'Of mice and mental health: facilitating dialogue between basic and clinical neuroscientists' convened by Amy Milton and Emily A. Holmes.

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