nature communications

Review article

https://doi.org/10.1038/s41467-025-57515-0

Endogenous opioid receptors and the feast or famine of maladaptive feeding

Received: 12 July 2024

Accepted: 21 February 2025

Published online: 06 March 2025

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Maladaptive feeding comprises unhealthy eating patterns that jeopardize survival, including over- and underconsumption. These behaviors are often coordinated by endogenous opioid receptors (EORs). Here, we explore the involvement of EORs in obesity and anorexia nervosa (AN), two disorders associated with dysregulated feeding behavior and relevant animal models. While seemingly opposing metabo-psychiatric states, our goal is to highlight common circuit and synaptic mechanisms underlying obesity and AN with a focus on EOR functionality. We examine the neural substrates underlying maladaptive feeding and comorbid conditions including pain, suggesting a role for EOR-driven plasticity in the pathogenesis of both obesity and AN.

Research over the past several decades has uncovered much about the role of endogenous opioid receptors (EORs) in neural circuits and feeding, including how such circuits may go awry in states with over- or under-consumption of food. Over- or under-consumption of food, while not always indicative of maladaptive feeding states can, when extreme, lead to diet-induced obesity or anorexia nervosa (AN), respectively. Obesity enhances excitatory transmission in the basal ganglia, mirroring the effects of exposure to drugs of abuse, and is believed to ultimately reshape the perceived value of food[1–3]. Valuation of food is also skewed in AN[4–8], and mouse models of activity-based anorexia (ABA) reveal structural and functional adaptations throughout the brain[9–13]. This implies that persistent dysfunction of brain circuits involved in feeding underlie maladaptive feeding states, though precisely how these circuits are aberrantly restructured and to what extent such changes overlap between the seemingly opposing conditions in obesity and AN is a subject of ongoing research. Our goal in this review is to outline well-studied phenomena surrounding EOR regulation of feeding in healthy conditions and to highlight areas of ongoing research pertaining to EOR dysfunction in AN and obesity. We will explore animal models and human studies, and form hypotheses about the role of EORs in AN and obesity, emphasizing where additional research is needed and potential future directions for the field.

EORs are highly expressed in brain regions implicated in obesity and AN, and human neuroimaging studies demonstrate that EORs are differentially expressed and/or demonstrate altered trafficking in individuals with obesity or AN[14–19]. In this narrative review, we postulate that dysfunction of EORs drives maladaptive feeding phenotypes as a primary node in both under- vs overconsumption. We review the established role of EORs in maladaptive feeding, highlight the overlap between pain sensation, comorbidities including substance use disorder, and hunger signaling across maladaptive feeding disease states, and hypothesize how EOR-linked mechanisms may underlie both AN and overeating leading to obesity (Fig. 1). The concurrent rise of obesity rates, prevalence of AN particularly among adolescents, and the opioid epidemic, highlight the critical need to understand the overlap of such circuit alterations.

Endogenous opioids and feeding

When examining the role of EORs in the development and persistence of maladaptive feeding states, one must first consider their ligands: endogenous opioids. These include a variety of peptides, classified based on their binding to EORs, that originate from multiple distinct brain sites within the brain. β-endorphin, which binds to both the mu-opioid receptor (MOR) and delta-opioid receptor (DOR), is derived from the proopiomelanocortin (POMC) gene, which is predominantly produced in the arcuate nucleus of the hypothalamus (ARC)[20,21]. β-endorphin increases feeding behavior via binding of MOR in the nucleus accumbens (NAc), while also decreasing food intake via binding of MOR in the ARC[22]. Beyond feeding, β-endorphin is a potent analgesic, playing a significant role in pain relief via MORs in the periaqueductal gray (PAG), among other brain regions[23]. β-endorphin binds MORs to drive the activation of the stress response coordinated by the hypothalamic-pituitary-adrenal (HPA) axis, while also

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https://doi.org/10.1038/s41467-025-57515-0

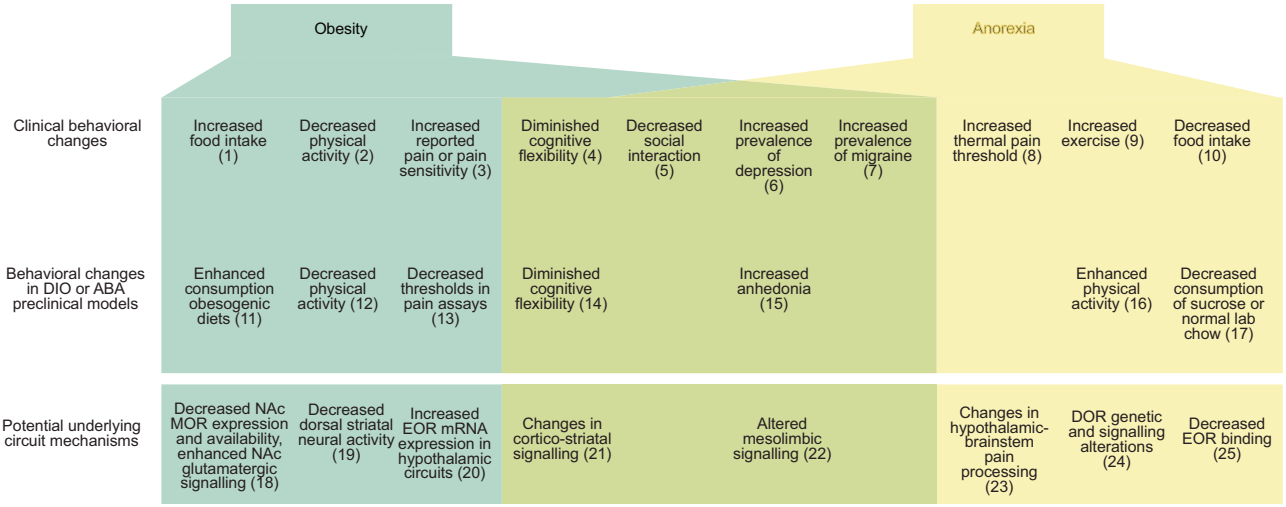

Fig. 1 | Obesity and anorexia have overlapping and distinct clinical symptoms and comorbidities. Preclinical rodent models support these observations and support potential neural circuit mechanisms underlying the spectrum of maladaptive feeding conditions. (1) Hall and Kahan[194]; Monda et al.[195]; Finkelstein et al.[196]; Swinburn et al.[197]; (2) Qiu et al.[198]; Berglind et al.[199]; (3) Bonomo et al.[124]; Guh et al.[123]; Okifjui and Hare[200]; Ray et al.[201]; McKendall and Haier[122]; (4) Perpina et al.[173]; Song et al., 2022[202]; Favieri et al.[203]; Zhang et al.[204]; (5) Vander and Mitchel[205]; Schaefer and Simpkins[206]; McAdams et al.[207]; Harrison et al.[208]; Troop and Treasure[209]; (6) Luppino et al.[210]; Sarwer et al.[211]; de Wit et al.[212]; Faith et al.[213]; Scott et al.[214]; Wade et al.[215]; Boehm et al.[216]; (7) Bond et al.[126]; Bigal et al., 2006[217]; Bigal et al.[218]; Bigal et al.[219]; Peterlin et al.[220]; Langowska-Grodzka et al.[221]; Mustelin et al.[222]; (8) Papezova et al.[223]; Lautenbacher et al.[128]; Lautenbacher et al.[224]; (9) Kaye et al.[9]; Spring and Bulik[8]; Holsen et al.[98]; Bewell-Weiss and Carter[225]; (10) Berkman et al.[226]; Frank et al.[227]; (11) Friend et al., 2017[228]; Licholai, et al.[229]; Yang et al.[230]; (12) Friend et al., 2017[228]; Matikainen-Ankney et al.[231]; (13) Roane and Porter[121]; Frick et al.[232]; (14) Labouesse et al.[233]; Labouesse et al., 2017[234]; Milton et al., 2021[10]; Conn et al.[235]; Wu et al.[236]; (15) Woodruff et al.[237]; Blaisdell et al.[238]; Seabrook et al.[239]; Sharma et al., 2013[240]; Hurley et al.[241]; Milton et al.[242]; Hurley et al., 2022[243]; Hurley et al.[241]; (16) Hall and Hanford[244]; Conn et al.[245]; Foldi et al.[246]; (17) Sutton Hickey et al., 2023[12]; Guitierrez[247]; Milton et al., 2021[10]; Perez-Padilla et al.[248]; (18) Burghardt et al.[14]; Karlsson et al.[15]; Ong et al.[68]; Robinson et al.[69]; Fritz et al.[175]; Alonso-Caraballo et al.[176]; Fetterly et al.[177]; Turcot et al.[178]; Matikainen-Ankney et al.[49]; (19) Friend et al., 2017[228]; (20) Pucci et al.[31]; (21) Dingess et al.[249]; Fetterly et al.[177]; Mottarlini et al.[250]; (22) Foldi et al.[251]; Segall and Margules[252]; Fordahl and Jones[253]; Sharma et al., 2013[240]; Vucetic et al.[86]; (23) Alhadeff et al.[120]; (24) Czyzyk et al.[91]; Bergen et al.[17]; Brown et al.[18]; (25) Galusca et al.[16].

coordinating anxiolytic responses to buffer the impact of stress, and thus titrate the overall stress response[21].

A separate endogenous opioid peptide is enkephalin, which includes leu-enkephalin and met-enkephalin. Enkephalins are predominantly produced in the striatum and exert their effects through binding MOR and DOR to coordinate hedonic feeding via NAc circuits and the ventral pallidum[24,25]. Enkephalins are widely recognized for their role in pain modulation since they are able to decrease pain transmission and perception in the spinal cord, amygdala, and insula to promote analgesia, stress reduction, and decreased HPA axis activation via both MOR and DOR[26].

Dynorphin A and dynorphin B, derived from the prodynorphin (*Pdyn*) gene, are endogenous opioids that are mainly produced in the hypothalamus and primarily act through KOR, with lower affinities for MOR and DOR[27]. Similar to enkephalins, dynorphins decrease pain responsiveness via the spinal cord, while also promoting dysphoria and aversion primarily via KOR activation in the NAc and prefrontal cortex (PFC) and inhibition of dopamine release in the midbrain[28]. Of particular interest to this review, dynorphins have been shown to drive feeding behaviors, though the directionality can be modulated depending on the emotional state of the animal, via binding to KOR[28]. Despite the extensive research highlighting the impact of endogenous opioid peptides on appetite, this review specifically focuses on the interaction between these peptides and their respective EORs in relation to maladaptive feeding states. EORs, which bind endogenous opioids and are influenced by their varying levels, are uniquely positioned to become dysregulated and thus may play a convergent role alongside endogenous opioids in both over- and under-consumption.

EOR function in the development of overeating leading to obesity

We need food to survive and thus the human brain has evolved to reinforce food seeking and consumption across motivational states. Highly palatable foods, typically with higher caloric value, are more reinforcing[29], which was likely evolutionarily advantageous in the scarcity environments human beings lived in for most of the past. In our current food landscape, these mechanisms now contribute to overeating and, oftentimes, corresponding weight gain. EORs are poised to exert lasting influence over food seeking and weight gain, illustrated by a genome-wide association study (GWAS) in French-Canadian adolescents that identified a preventative effect against fat consumption and adiposity associated with a minor allele of the *Oprm1* gene[30], encoding the MOR. Conversely, decreased methylation of the *Oprm1* promoter was observed in individuals with obesity compared to healthy controls in peripheral blood DNA[31]. This suggests that EORs, and MOR in particular, may play an important role in regulating food intake and overeating.

Pharmacological studies further implicate EORs in feeding and bodyweight regulation. Naloxone, a broad opioid receptor antagonist, has been shown to have an anorectic effect in humans[32] and rodents[33] and suppressed the consumption of sweetened milk in both obese and normal-weight women[34]. Furthermore, inhibiting EORs in combination with antidepressants, such as those combining bupropion (a norepinephrine-dopamine reuptake inhibitor; referred to as Wellbutrin) and naltrexone (an opioid receptor antagonist with high affinity for MOR and to a lesser extent DOR and KOR) treatments, promoted weight loss in overweight or obese individuals[35,36]. Research in rodents corroborates these findings; studies in the 1960s-1970s demonstrated systemic administration of morphine or amphetamine, both EOR agonizts, increased chow intake[37,38]. In contrast, opioid receptor antagonists decreased rodent intake of the infant formula Enfamil[39]. Subsequent studies built on these findings to demonstrate that EORs selectively drive the consumption of highly palatable foods. Intraperitoneal injection of naltrexone in rats reduced highly palatable cafeteria diet intake but did not affect regular chow consumption[40]. With the advent of knock-out mouse models, researchers discovered that

eliminating MOR globally in mice did not affect normal feeding behavior on a standard diet, but when provided with an obesogenic high fat diet (HFD), mice were resistant to diet-induced obesity[41]. DOR knockout mice underperformed on an operant task for chocolate sucrose pellets relative to controls[42]. Similar results were observed with the global deletion of kappa opioid receptors (KOR) in mice, in which diet-induced obesity was also mitigated[43]. Together, these studies demonstrated that globally inhibiting or removing EORs reduced seeking of palatable foods, underscoring a potent role for EORs in food intake.

One theory of hedonic feeding posits that central signals from the NAc, a region in the basal ganglia implicated in reward and motivation, drive overconsumption[44–46]. Activating or inhibiting the two primary projection neuron populations in the NAc, D1-SPNs or D2-SPNs, or their inputs, bidirectionally modulates food seeking or consumption[47–50]. This suggests that changes in circuit-specific activity in the NAc drive changes in feeding behavior, similar to the documented enhancements in basal ganglia connectivity following exposure to drugs of abuse[51]. EORs are well-positioned to exert lasting influence on accumbal feeding circuits. MOR, DOR, and KOR are all robustly expressed in the NAc[46,52–55], and decades of research demonstrate their involvement in hedonic food intake[56]. In the late 1990s, research from Anne Kelley's research group demonstrated that bidirectional modulation of endogenous MORs in the NAc increased or decreased consumption of sucrose but not standard chow diet in rats[54,57,58], and direct injection of DOR-specific agonizts into the NAc enhanced sucrose consumption[54]. Further, multiple studies demonstrated that injection of pan-EOR or MOR-specific agonizts into the NAc resulted in increased consumption of high-calorie food[56,59–61]. Taken together, this work supports a model for feeding in which NAc EORs drive coordinate palatable food intake, which aligns with broader literature suggesting NAc EORs are crucial for reward processing[62]. This is further supported by the observation that while MOR knockout mice are prone to obesity when exposed to a normal chow diet, they are more resistant to weight gain with exposure to a high-fat diet relative to wild-type controls[63].

However, alongside these findings, antagonist experiments targeting NAc EORs provide mixed support for their role in driving palatable food consumption. Infusion of a MOR antagonist into the NAc attenuated responding to food cues[64], and NAc-directed infusion of naltrexone reduced consumption of high-calorie foods[58,65,66], supporting a role for MOR in the seeking and consuming of rewarding food. However, lower dose infusions of MOR antagonists into the NAc reduced standard lab chow consumption in fasted rats[66]. This speaks to a broader role for NAc EORs in high-value food consumption and highlights that a high value may be assigned to a food based on either homeostatic need, as in the case of chow during a hunger state[49], or caloric density, as with the perceived high-value of calorically dense foods[3]. Another study found no effect of MOR antagonist injection into the NAc on high-calorie food consumption, yet this study examined liquid consumption in an intermittent-access paradigm[60]. Such a paradigm likely involves varied behavioral strategies distinct from the consumption of freely available food[67].

Studies of MOR availability in obesity further support a link between accumbal MOR and overeating leading to weight gain. Positron emission tomography (PET) scans demonstrated that individuals with obesity have lower levels of MOR availability in the NAc[14,15], and rodents exposed to obesogenic diets exhibited decreased MOR mRNA in the NAc[68], specifically in obesity-prone rats[69]. These results are somewhat counterintuitive, as one might expect conditions of obesity, in which palatable food consumption is higher than in non-obese conditions, to be associated with increased MOR receptor availability based on the preclinical research in rodent models outlined above. However, a study of healthy-weight Finnish individuals revealed a link between decreased cerebral MOR binding availability and increased self-reported palatable food consumption behaviors, suggesting that less MOR availability is associated with enhanced feeding[70]. This also highlights the disconnect between assays that modulate MOR in healthy-weight animals and measure food intake and observational readouts of MOR availability or transcription in obese conditions. While there appears to be a role for MOR in the overconsumption of foods, additional studies are required to link the mechanisms of aberrant MOR function during exposure to obesogenic environments that might promote continued food seeking and maladaptive weight gain.

Separate from the pursuit of highly palatable food, feeding based on hunger or satiety signals is thought to rely predominantly on hypothalamic circuits[71]. The role of EORs in the hypothalamus is less understood relative to their role in mesolimbic circuits. EORs exhibit diverse expression in hypothalamic subregions, with MORs broadly expressed in the suprachiasmatic nucleus (SCN), lateral hypothalamic area (LHA), dorsomedial hypothalamus (DMH), and to a lesser extent in the arcuate nucleus (ARC) and the preoptic area (POA)[72–74]. KORs show robust expression in the SCN, ventromedial hypothalamus (VMH), LHA, paraventricular hypothalamus (PVH), and ARC[73–76], while DORs are most present in the SCN, VMH, ARC, and paraventricular hypothalamus (PVH)[73,74,77]. Over the past three decades, research has begun to link opioid release in the hypothalamus with its well-described role of controlling feeding behavior, focusing on how EORs affect hunger- and satiety-promoting circuits[78]. Hunger-promoting agouti-related peptide (AgRP) neurons in the ARC and downstream melanocortin pathways, such as those in the PVH and LHA, are influenced by EORs. Local administration of EOR agonists in these regions increases feeding, while antagonists decrease it[79,80]. Specifically, MOR agonist injection in the PVH increases feeding, whereas blocking MOR or KOR, but not DOR, in the PVH reduces fasting-induced food intake. Additionally, naloxone administration blocks AgRP-induced food intake[81]. While these studies suggest that homeostatic feeding mechanisms are impacted by EORs to promote feeding, a recent study confounds these findings by demonstrating that endogenous opioids, which are increased in the ARC following the consumption of various diets, inhibit AgRP neurons via MORs[82]. These findings highlight the complex and context-dependent role of EORs in regulating hypothalamic circuits and feeding behavior, suggesting that their influence on homeostatic mechanisms may vary depending on physiological state and dietary context. Lastly, while the mechanisms underlying site and cell-type specific EOR function in the hypothalamus are complex, it seems likely they are implicated in obesity. In contrast to what is seen in the NAc, studies suggest obesity is associated with an increase in MOR expression in the hypothalamus; rats exposed to *ad libitum* HFD had a transient increase in MOR mRNA after 5 weeks compared to rats fed a control diet[31]. Additional studies are required to parse ongoing effects of increased hypothalamic EOR expression on chronic overconsumption of palatable diets and the corresponding development of obesity.

Collectively, these studies support a model in which EORs expressed in NAc and hypothalamic neurons regulate palatable food consumption. As such, aberrant activity of EORs may subsequently promote overeating leading to obesity, though such directionality—over- vs under-eating—is highly contextual, and the extent to which EORs coordinate intake across dietary choices remains understudied. Furthermore, studies of obesity in animal models employ a range of diet contents including sugar, fat, and carbohydrates. While all these diets are considered palatable, it is intriguing to consider that the coordination of palatable food intake might be separable across NAc or hypothalamic EORs depending on diet composition and content (e.g., perhaps DOR preferentially controls sucrose consumption while MOR drives fat seeking), as there is precedent for different macronutrients differentially driving food intake and behavior[83,84]. Furthermore, the link between NAc and hypothalamic EOR stimulation and feeding appears to vary as a function of longitudinal exposure to HFD. Acute EOR stimulation in the NAc and hypothalamus drives intake of

https://doi.org/10.1038/s41467-025-57515-0

palatable food; yet chronic HFD exposure decreases NAc EOR expression[85,86] but increases hypothalamic EOR activity[87]. This suggests that long-term HFD exposure may involve distinct, region-specific neurobiological mechanisms.

EORs and AN

A prominent feature of eating disorders, particularly AN, is the substantial heritability of the condition, with estimates ranging from 56% to 84% contingent on the methodology used[88]. This high heritability has spurred numerous genetic studies to identify potential hereditary factors involved in AN pathogenesis. Genome-wide association studies (GWAS) have pinpointed a specific linkage region (1p33-36) that includes the candidate gene delta opioid receptor 1 (*Oprd1*) as a possible genetic susceptibility locus for AN[17,18,89]. Associations between *Oprd1* and AN have been observed across both restricting and binge-purging subtypes, further implicating DOR in the abnormal feeding behaviors characteristic of AN[18]. Although further research with larger sample sizes is needed to pinpoint specific SNPs driving AN heritability, a meta-analysis of existing studies found a strong association between genetic disruptions in *Oprd1* and AN pathogenesis[19]. However, the precise alterations in *Oprd1* gene expression in AN remain unclear. In rodent models, global elimination of DOR using *Oprd1* knockout mice results in increased physical activity, anxiety, and depressive-like behavior[90], and DOR knockout mice are resistant to diet-induced weight gain[91]. These effects are blunted by naloxone administration[90], suggesting that the adverse outcomes of DOR deficiency can be mitigated by antagonizing other EORs, which might become overactive in response to the absence of DOR. While not specific to DOR, PET imaging in humans experiencing AN demonstrated decreased EORs across multiple brain regions implicated in reward and aversive responding, including the midbrain, NAc, and amygdala[16].

Research on altering opioidergic circuits in the brain highlights their potential as therapeutic targets for AN, especially in addressing feeding-related abnormalities and comorbidities. Opioid receptor antagonists have been proposed as AN treatments for over four decades[92,93], when Marrazzi et al. posited that AN functions as an auto-addiction disease, in which dieting triggers endogenous opioid release, ultimately reinforcing dieting behavior[92,94,95]. In response to dieting/starvation, opioids typically promote food intake, leading to an acute adaptive response to increase intake and promote body weight maintenance. However, in the case of AN, this theory posits that the initial "high" elicited by starvation disrupts normal functioning and leads to an addiction to starvation. The lack of food intake in response to starvation-induced opioid release may in turn drive subsequent maladaptive behaviors, such as increased exercise, thus promoting a reinforcing feedback loop (Fig. 2)[96]. The existence of such a feedback loop is supported by evidence showing that vigorous, sustained exercise decreases opioid receptor binding in frontal cortical and limbic brain 'reward' nuclei in PET scans of healthy male subjects, suggesting such exercise may flood the brain with endogenous opioids[96]. Indeed, increased physical activity is a common characteristic of AN, occurring in up to 80% of AN patients[8,9,97,98], and elevates endogenous opioids like β-endorphin[99]. Compulsive exercise in AN stands to amplify endogenous opioid release, reinforcing the behavior while simultaneously de-prioritizing food intake, ultimately contributing to severe weight loss. Evidence from concurrent rodent studies supports this theory, since researchers discovered that animals given access to a voluntary running wheel, while simultaneously food-restricted, developed robust hyperactivity and weight loss (termed activity-based anorexia (ABA)), mimicking a subset of human AN behaviors[9,100].

Hypotheses suggest that food restriction in rodents is stressful and anxiety-provoking[101–103], and exercise may mitigate this anxiety through endogenous opioid release and corresponding EOR activation. While studies in animal models cannot fully replicate the heterogeneity of AN, these findings propose a potential model where exercise-induced opioid release mirrors the addictive patterns seen in opioid use. Rats with running wheel access show diminished sensitivity to opioids, likely due to elevated endogenous opioids causing a "ceiling effect" of antinociception[104–106]. Diminished conditioned place preference for morphine in animals with running wheel access in their homecage further suggests that exercise elevates baseline EOR activity, limiting additional opioid efficacy in driving preference[107]. Further, MOR activity is required for the increases in food anticipatory physical activity observed in response to food restriction, but not for body weight maintenance during these conditions[108,109], suggesting MORs coordinate physical activity increases observed in response to hunger. A mechanism for this effect might be via MORs on AgRP neurons, which work to suppress AgRP neuronal activity, and thus feeding[82]. While this specific mechanism has not been interrogated in the regulation of physical activity, decreased AgRP activity has been shown to promote increased physical activity[12], and thus body weight loss, in ABA. Yet, whether increased MOR activation and/or increased activity of other EORs is the mechanism coordinating these maladaptive behaviors in ABA (and AN) has not been fully interrogated.

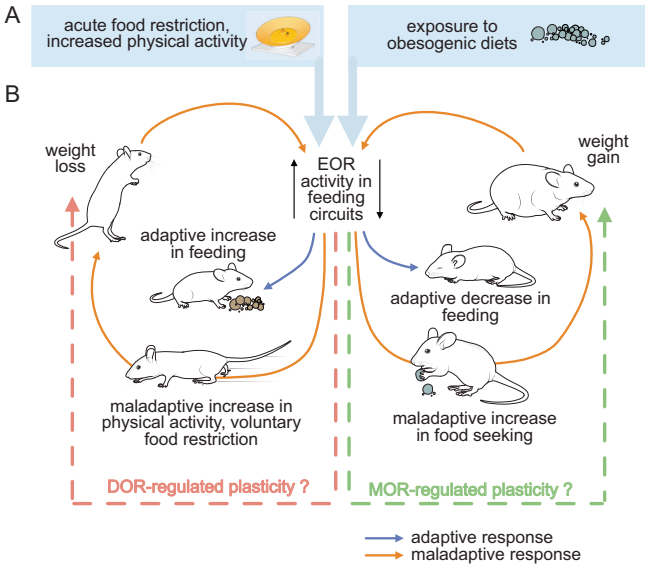

Fig. 2 | Plasticity mechanisms potentially underlie chronic maladaptive feeding. a Initial exposure to either obesogenic diets or food restriction combined with physical activity (**b**) starts maladaptive cycles of weight gain (right) or loss (left) that correspond to decreased or increased EOR activity in feeding circuits (orange arrows). We posit that enhanced or diminished feeding states initially engage EOR-mediated plasticity mechanisms that further drive maladaptive feeding including enhanced food seeking, or excessive physical activity, and diminished caloric consumption.

Taken together, it is plausible that distinct endogenous opioids affect separate AN outcomes. Anticipatory behaviors associated with food reward may be coordinated by MOR-dependent systems[65,108,110], whereas satiety-mediated feeding behaviors are potentially modulated by DOR[46,111]. Both require further investigation to understand the implications for the genetic alterations identified in AN patients (e.g., *Oprd1*) and their impact on feeding, exercise, and body weight outcomes. While EOR availability is altered in AN[16], studies have largely been inconclusive in determining whether endogenous opioid levels are altered in AN, partially due to the challenges in measuring brain opioid levels in AN patients[112–117]. The studies that do exist suggest that the potential of antagonizing EORs as a treatment for AN remains plausible, with promising results with naloxone driving increased fat consumption in rodents, and naloxone or naltrexone treatment in AN patients facilitating improved weight gain[92,93,118].

EORs in brain circuits at the intersection of maladaptive feeding and pain

Pain is a comorbidity in maladaptive feeding, and feeding behaviors are deeply intertwined with both pain and hunger. Pain can suppress appetite[1,119], while hunger, particularly during caloric deficit, can override nociception[120]. This bidirectional relationship is particularly complex in obesity and AN, where both pain perception and feeding behaviors are often dysregulated. In obesity, pain is more prevalent and frequently dysregulated, observed in both human and animal studies[121–124]. This could be partly due to musculoskeletal stress from increased adiposity[125], though non-kinematic pain types like chronic migraines are also more prevalent in obesity[126]. Preclinical models investigating pain, including migraine, remain underexplored in the context of obesity[127]. In contrast, individuals with long-term AN often exhibit increased pain thresholds, a phenomenon not observed in healthy individuals that are merely fasted[128,129]. This suggests that chronic undernutrition, rather than acute bouts of fasting, might drive these alterations in pain sensitivity in AN. Identifying whether heightened pain sensitivity plays a role in AN development in humans is methodologically challenging, complicating the distinction between decreased pain responsiveness observed in AN due to life events (e.g., enhanced fear responsiveness, a key clinical feature of AN) or increased pain signals. Rodent models interrogating the intersection of pain and anorexic behaviors have shown mixed results: ABA rats displayed decreased pain thresholds for mechanical stimuli but increased thresholds for thermal stimuli[130]. Other studies in mice revealed that acute fasting reduces nociception, with pain responsiveness negatively correlating with fasting duration[131]. Chronic caloric restriction similarly decreases nociception to mechanical and thermal stimuli, mirroring observations in AN[132].

Circuits implicated in maladaptive feeding are strongly linked to pain, such as the parabrachial nucleus (PBN), ARC, and the NAc. The PBN is connected to vagal and homeostatic pathways that coordinate satiety, and midbrain structures (e.g., periaqueductal gray) that coordinate pain responses. Hypothalamic hunger-promoting AgRP neurons project to the PBN and modulate responses to inflammatory pain[120], potentially via MOR expression on AgRP neurons[82]. AgRP neuronal responses to cold are blunted in animals with HFD access[133], suggesting obesogenic diets may also affect thermal pain perception. In AN, theories posit that altered brain circuitry or vagal input might suppress hunger-related pain signals, such as hunger pangs, though it's unclear if heightened pain sensitivity is a cause or result of the disease, or if EORs underlie these processes[134,135]. The NAc, which encodes affective value of food, plays a key role in pain processing (reviewed in[136]), with chronic pain conditions linked to dysregulated NAc activity[136,137]. Altered NAc activity and blood flow are also associated with migraine in humans[136,138]. This dysregulation is potentially mediated by EOR activity in the NAc, since chronic pain can be ameliorated or accelerated by NAc KOR inhibition or activation, respectively[139]. The NAc is also involved in pain processing circuitry through inputs from the basolateral amygdala, ventral tegmental area, and ventral pallidum[140–142]. EORs are either directly expressed in these NAc inputs to influence behavioral outcomes[141], or activity of these inputs is capable of modulating NAc EOR availability to induce behavioral effects[142–144]. Neuromodulation studies further support the role of the NAc in both pain and food intake. Deep brain stimulation (DBS) has been used off-label to treat chronic pain for over 60 years, typically targeting regions like the periaqueductal grey, thalamic nuclei, or anterior cingulate cortex (ACC)[145], and projections from the ACC to NAc drive pain aversion in mice[146]. While rare, case studies show that direct NAc stimulation can relieve pain[147], and clinical studies have shown improvements in pain processing through DBS targeting the ventral striatum/internal capsule[148]. NAc DBS has also been explored as an obesity treatment, inducing weight loss and reducing food intake in both humans and rodents[149–151]. While chronic NAc DBS in mice diminishes food intake[152], significant weight loss is not always observed, underscoring how varying stimulation paradigms may drive different outcomes in the short- vs long-term. Further, NAc DBS has been used in at least one case as a treatment for AN in adulthood, suggesting that targeting dysregulated NAc circuits with DBS can treat underlie both obesity and AN[153,154]. While promising, these studies are preliminary and lack the preclinical research necessary to uncover how brain circuits that are altered in obesity, AN, and acute versus chronic pain influence one another. Furthermore, it is not known if the preliminary beneficial effects observed in response to NAc DBS on obesity and/or AN are via alterations in EOR levels or binding in the NAc, though DOR-mediated plasticity is hypothesized to play a role[155].

Addiction, maladaptive feeding, and EORs

Substance use and/or abuse and maladaptive feeding are often interconnected, as substance use can both acutely and chronically alter feeding patterns[156], and conversely, feeding patterns can influence the perceived effect of drugs. One example of this phenomenon is the body's response to food restriction, which can increase drug sensitivity. For instance, the persistence of morphine-induced conditioned place preference is enhanced in conditions of food restriction in rats, suggesting hunger further incentivizes the positive affect associated with opioid use[157]. Chronic food restriction enhances reward magnitude and locomotor-induced drug effects[158–160]. These studies suggest chronic hunger promotes susceptibility to substance use.

Indeed, the comorbidity of AN and substance abuse disorder is high, with approximately 27% of individuals with AN also meeting the criteria for SUD[161]. Binge-eating disorder, which can involve repeated periods of food restriction, is linked to substance use disorder (SUD)[162,163]. A recent study of more than 400,000 college students revealed that among individuals diagnosed with eating disorders, including AN, there was a significant increase in the risk of SUD including opiate misuse[164]. Further, the degree of caloric restriction in eating disorders, regardless of type, is positively correlated with an increased propensity for substance use[165]. Thus, studies of individuals with eating disorders support a link between chronic hunger states and substance use or misuse.

The relationship between obesity and substance use or misuse is less well-defined. However, there is an overlap in brain activation patterns observed in individuals with obesity compared to those with SUD, suggesting common underlying neurobiology[166]. Overeating leads to obesity is often discussed as "food addiction", in which the overconsumption of food is considered within a framework of compulsive behavior that mimics what is observed in SUD[167,168]. This supports a broader model wherein maladaptive feeding is associated with dysregulated impulse control and risk-taking behavior[169,170]. Feeding patterns including post-surgical food reduction in obese states may contribute to substance misuse. For example, gastric bypass surgery is associated with increased risk of onset of opioid use in individuals that includes but is not entirely due to post-surgical pain[171,172]. However, as with AN and restrictive feeding disorders, a clear connection between overeating leading to obesity and development of SUD requires additional investigation.

EOR-driven plasticity mechanisms in AN and obesity

While seemingly opposing disease states, the studies outlined here demonstrate that shared EOR-linked mechanisms potentially underlie the maladaptive feeding behaviors present in both AN and obesity. From an evolutionary standpoint on energy intake, overlapping brain circuits coordinating over- and under-consumption of food is advantageous, since bi-directional adaptive responses to varying environmental shifts (e.g., lack of food availability, predator evasion, seasonal shifts in ambient temperatures) require the cognitive flexibility typically associated with enhanced neural plasticity. Indeed, a shared key

behavioral characteristic of AN and obesity is a lack of cognitive flexibility in adaptive food intake[173,174], and plasticity mechanisms are dysregulated in both AN and obesity. Specifically, exposure to obesogenic diets increased AMPA/NMDA ratios in mice[175], and withdrawal from obesogenic diets enhanced calcium-permeable AMPA receptor (CP-AMPAR) recruitment in the NAc core of rats[176,177], suggesting the induction and maintenance of long-term potentiation (LTP) is modulated by exposure to obesogenic diets. A 2018 GWAS implicated a subunit of the NMDA receptor - also involved in plasticity mechanisms - in obesity[178], and recently GLP-1 agonist-delivery of NMDAR antagonists induced weight loss in mice at a greater rate than GLP-1 agonism alone[179], suggesting control of synaptic plasticity in satiety circuits as a weight loss therapeutic. Ketamine-induced increases in synaptic NR2B, an NMDAR subunit, in the mPFC correlated with increased food consumption in ABA mice[180], and extensive synaptic and morphological changes were recorded in excitatory and inhibitory hippocampal neurons in rats and mice on the ABA paradigm[181,182], demonstrating aberrant plasticity mechanisms in ABA. Interestingly, both acute food restriction *or* brief exposure to high-fat diet increased inhibitory LTP in NAc projections to the lateral hypothalamus (LH)[183], further underscoring the idea that opposing feeding states can induce overlapping plasticity changes, likely via long-term plasticity changes at glutamatergic synapses in reward brain circuits.

Plasticity mechanisms are driven by EOR function, and expression of MOR[46,52–54], KOR[46,55], and DOR[46,54], are enriched in the NAc and hypothalamus. Stimulation of MORs induced striatal long-term depression (LTD) in ex vivo rodent studies[184,185], KOR agonists increased expression of synaptic proteins (NR2B, GluR1, PSD95 and SYN) in mouse hippocampal tissue[186] and abolished STDP-LTP in D1 SPNs in dorsal striatum[187], and DORs drove LTP in the hippocampal mossy fiber pathway in female rats[188] and LTD in striatum[184]. Further, rodent and human studies support that MORs in the NAc are significantly altered in obesity, and DOR (and potentially MOR) might be altered in AN, as discussed above. As MOR and DOR drive LTD[184], this suggests diminished opioid receptor expression, availability, or function during obesity or AN may spur dysfunctional LTD, similar to occluded NAc plasticity after exposure to heroin[189] or cocaine[190]. Indeed, rodents given a Western diet showed ablated DAMGO-mediated LTD in dorsal striatum[175], suggesting that Western diets disrupt MOR-mediated striatal plasticity. Thus, the synaptic physiology coordinating under- or over-consumption of food converges on altered EOR action in accumbal and hypothalamic circuits, suggesting EORs are poised to modulate plasticity in maladaptive feeding states (Fig. 2). However, the extent to which disrupted plasticity in feeding circuits contributes to persistent increases or decreases in food-seeking remains unknown, and more work is needed to place maladaptive feeding-linked synaptic changes in the context of normal synaptic plasticity. While much of our knowledge about long-term plasticity comes from studies examining the roles of NMDARs and AMPARs in LTP and LTD at glutamatergic synapses in the dorsal striatum or hippocampus of healthy controls, maladaptive feeding states likely invoke novel plasticity mechanisms. For example, mGluR5-dependent LTD in hypothalamic orexin neurons was unmasked by exposure to an obesogenic diet[191]. Regardless, these studies support a model of maladaptive feeding in which aberrant plasticity mechanisms in precise feeding circuits may drive lasting behavioral change.

Conclusions and limitations of the review

Collectively, these studies indicate EOR-circuit modulations may underlie behavioral features observed in obesity and AN, including over- and underconsumption, altered physical activity and motivation, and pain responsiveness. We propose EOR-linked plasticity in brain circuits, which is relevant across the development of multiple disease states, as a key contributing factor in both obesity and AN. We highlight multiple brain regions and circuitry (e.g., NAc, hypothalamus, among others) where EORs are highly expressed, have been linked to feeding, and exhibit expression or binding availability changes in human or rodent models of obesity or AN. We outline how future studies are required to understand the exact interplay between EORs, dysregulated feeding, pain processing, substance misuse, and the directionality of disease states associated with these comorbid phenotypes.

The scope of this review is limited to EORs, yet obesity and AN are complicated disorders overlying multiple brain mechanisms and likely involving independent processes. As just one example, melanocortin 4 receptor (MC4R) has been identified in the development of monogenic obesity[192]. While monogenic obesity accounts for only 0.1–5% of extreme obesity in humans[193], this speaks to the existence of varied mechanisms driving feeding disorders. Similarly, EOR expression is not limited to the NAc and hypothalamus, and EORs are expressed in additional brain circuits are associated with feeding. While the examination of these additional circuits and varied genetic landscape is beyond the scope of this review, we must consider our hypothesis that EOR-induced circuit dysfunction drives obesity and AN in a broader context beyond the putative "hedonic" accumbal and "homeostatic" hypothalamic feeding circuits.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

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Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-025-57515-0.

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Peer review information *Nature Communications* thanks Bogdan Galusca and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

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