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Similarities in hypothalamic and mesocorticolimbic circuits regulating the overconsumption of food and alcohol

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Abstract

Historically, studies of food intake regulation started with the hypothalamus and gradually expanded to mesocorticolimbic regions, while studies of drug use began with mesocorticolimbic regions and now include the hypothalamus. As research on ingestive behavior has progressed, it has uncovered more and more similarities between the regulation of palatable food and drug intake. It has also identified specific neurochemicals involved in palatable food and drug intake. Hypothalamic orexigenic neurochemicals specifically involved in controlling fat ingestion, including galanin, enkephalin, orexin and melanin-concentrating hormone, show positive feedback with this macronutrient, with these peptides both increasing fat intake and being further stimulated by its intake. This positive relationship offers some explanation for why foods high in fat are so often overconsumed. Research in Bart Hoebel's laboratory in conjunction with our own has shown that consumption of ethanol, a drug of abuse that also contains calories, is similarly driven by these neurochemical systems involved in fat intake, consistent with evidence closely relating fat and ethanol consumption. Both fat and ethanol intake are also regulated by dopamine and acetylcholine acting in mesocorticolimbic nuclei. This close relationship of fat and ethanol is likely driven in part by circulating lipids, which are increased by fat and ethanol intake, known to increase expression and levels of the neurochemicals, and found to promote further intake of fat and ethanol. Compellingly, recent studies suggest that these systems may already be dysregulated in animals prone to consuming excess fat or ethanol, even before they have ever been exposed to these substances. Further understanding of these systems involved in consummatory behavior will allow researchers to develop effective therapies for the treatment of overeating as well as drug abuse.

Keywords

fat; ethanol; lipids; hypothalamus; mesocorticolimbic; peptides

1. Introduction

The idea that consumption of palatable food and drugs is mediated by similar brain circuitry has received a great deal of attention in recent literature. Imaging studies have begun to identify overlapping circuits activated by this intake [1–3] and focus attention on central reward mechanisms as a common link. It is now accepted that food, in addition to satisfying

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a demand for energy, can also be consumed for its hedonic qualities, a concept proposed in a pioneering study by Bart Hoebel and Philip Teitelbaum [4]. Further, alcohol, in addition to being consumed for its rewarding properties, can also be consumed for its caloric value. Although it is now becoming clear that both hypothalamic and mesocorticolimbic brain regions similarly regulate the consumption of certain foods, such as those rich in fat, as well as of drugs of abuse, such as alcohol, research in the feeding and drug fields initially progressed from very different regions in the brain (Figure 1).

1.1. Feeding research

The hypothalamus was established as early as the 1920s as important in the control of food intake [5–7]. As research in the field progressed, it became apparent that specific nuclei within the hypothalamus and specific neurochemicals within these nuclei were responsible for fluctuations in feeding behavior. Hetherington and Ranson established the medial hypothalamus as a “satiety center” [8], and later, Anand and Brobeck described the lateral hypothalamus as a “feeding center” [9]. Following this, biogenic amines and peptide transmitters, such as opioids and galanin (GAL), were found to act in the paraventricular nucleus of the hypothalamus (PVN) to stimulate food consumption [10–12]. At the same time, neuropeptide Y (NPY) within the nearby arcuate nucleus (ARC) was shown to tightly regulate feeding behavior in response to signals from hypophyseal portal circulation [13–15]. More recently, peptides such as orexin (OX) and melanin-concentrating hormone (MCH), which are produced in the perifornical lateral hypothalamus (PFLH), were also found to have a significant role in energy balance [16–18]. Although these peptides primarily regulate feeding behavior based on energy demand, they also appear to promote non-homeostatic or reward-driven feeding in an environment with excess availability of palatable, energy-rich foods.

As it became clearer that certain foods were consumed for their reinforcing value, it was recognized that limbic regions connected with the hypothalamus could also influence food intake [19], particularly when palatable food was involved [20]. Initial research pioneered by Bart Hoebel and colleagues as well as others concluded that feeding and/or food reward could stimulate dopamine (DA) release within the nucleus accumbens (NAc), a primary site for reinforced behaviors [21–23]. The opioid peptide, enkephalin (ENK), was also found to function within this region to stimulate consummatory behavior, particularly when fatty foods were available [24–26]. Collectively, these studies demonstrate that the field of food ingestion, while originating with the hypothalamus, grew to include mesocorticolimbic regions that regulate rewarding food intake.

1.2. Alcohol research

In parallel with research on feeding, studies on drug reinforcement were also being conducted. The mesolimbic DA pathway, originating in the ventral tegmental area (VTA) and projecting to the NAc, was regarded as the primary substrate of reward-related behavior, which included the consumption of abused drugs such as alcohol. The rewarding properties of these drugs were strongly and positively correlated with the actions of DA in the NAc [27–29], with numerous studies pointing to the VTA and NAc as the primary drug reward centers [30]. While it has been known since the later 1950s that the lateral hypothalamus was also intimately involved in reward [31, 32], it was not until the 1970s that scientists demonstrated that lateral hypothalamic stimulation could trigger ethanol consumption [33, 34]. More recent studies performed in the Hoebel and Leibowitz laboratories have since demonstrated that hypothalamic peptides, including GAL, ENK, OX and MCH, could also stimulate ethanol intake [35–37]. Thus, the path of research in the alcohol field, while originating with mesolimbic circuits, grew to encompass the same hypothalamic regions

known to regulate feeding behavior, specifically those controlling the consumption of palatable food.

1.3. Networks between hypothalamic and mesocorticolimbic regions

Building on the similarity in the nuclei governing the consumption of palatable food and drugs of abuse, much recent research has been devoted to delineating the neuronal networks that promote the ingestion of these substances. Neurochemical networks exist both within the hypothalamus and between hypothalamic and mesocorticolimbic nuclei, often with reciprocal connections between the areas (Figure 2). Within the hypothalamus, the ARC lies adjacent to the median eminence and detects changes in peripheral signals, such as glucose and lipids. The “first order” NPY neurons of the ARC then project to “second order” neurons in more dorsal regions of the hypothalamus, such as those containing GAL and ENK in the PVN [38] and OX and MCH in the PFLH [39]. While OX and MCH interact with each other [40, 41], they also project to the PVN [42–44], where OX at least appears to stimulate ENK [45].

Hypothalamic projections can also extend to regions outside of the hypothalamus. Projections from the PVN, which mostly contain corticotrophin releasing factor as well as the opioid ENK, terminate in part in the VTA [46, 47]. Projections from the PFLH, which contain OX or MCH, have been shown to extend to limbic regions, such as the NAc [48] and, in the case of OX, also to the VTA and prefrontal cortex (PFC) [49]. In return, the NAc, VTA and PFC project back to the hypothalamus [50–52] to regulate neurochemical signaling.

With such overlap in the circuitry governing palatable food and drug intake, this review will start by describing several neurochemical systems common to their intake. In many cases, these neurochemicals both drive intake and are also stimulated by intake, pointing to the existence of positive feedback loops that can lead to overconsumption. It will then discuss how lipids circulating in the blood may be responsible for the similarity between palatable foods high in fat and drugs such as ethanol. Finally, it will summarize exciting new findings that these same systems, which are disturbed by palatable food and drug intake and themselves drive intake, may already be disturbed early on in certain animals prone to overconsuming these rewarding substances. Work by Bart Hoebel and his colleagues over the years has contributed significantly to our current knowledge in this field.

2. Regulation of palatable food overconsumption

Palatable foods include those that are made with the dietary macronutrient fat, and high-fat foods are almost invariably overconsumed. This may be due to fat’s caloric density and texture, although fat has also long been known to be less satiating than protein or carbohydrate [53]. Fat-induced hyperphagia is particularly evident in acute feeding paradigms, with a high-fat compared to low-fat meal followed by a shorter post-meal interval and larger subsequent food intake [54–56]. Certain neurochemicals in the hypothalamus and mesocorticolimbic areas have been associated with palatable food intake in general, and some of these appear to be specifically related to fat intake.

2.1. Hypothalamic peptides and palatable food consumption

2.1.1. The arcuate nucleus—The major orexigenic peptide within the ARC is NPY. Expression and levels of this peptide rise immediately prior to scheduled feeding as well as during food deprivation [57, 58], and hypothalamic injection of NPY potently stimulates food intake [15, 59]. When given a choice between diets with different macronutrient content, rats injected with NPY increase their carbohydrate rather than fat intake [59, 60], so

this peptide appears to be more important in the consumption of foods high in sugar than those high in fat. While the immediate, short-term effects of carbohydrate intake are to decrease hypothalamic NPY expression [61, 62], it ultimately results in higher NPY over the long term [63, 64], which may explain why sugary foods are also overconsumed.

2.1.2. The paraventricular nucleus—Two major orexigenic peptides within the PVN are GAL and ENK. In contrast to NPY, these peptides share a close relationship with foods high in fat rather than those high in sugar. Like NPY, hypothalamic expression and levels of GAL rise during food deprivation [65], and injection of GAL into the hypothalamus stimulates food intake [66, 67], although these effects, including the increase in GAL, are smaller and of shorter duration than for NPY [68]. The feeding induced by GAL injection, however, is stronger and more prolonged in subjects maintained on a high-fat compared to a low-fat diet [69]. Also, gene expression and peptide production of GAL in the PVN is stimulated by consumption of dietary fat, but not by carbohydrate or protein [70, 71], suggesting that GAL could mediate the overconsumption of fatty foods. This idea is particularly supported by findings in genetically modified mice, which show that GAL overexpressors, despite having similar laboratory chow intake, consume more fat, whereas GAL knockout mice consume less fat than wild-type mice [72–74].

Much as with GAL, hypothalamic injections of ENK agonists stimulate food intake [75, 76], and PVN injection of an ENK analogue acting at the mu receptor selectively increases intake of a high-fat diet over a sucrose diet [77]. Hypothalamic expression and levels of ENK are also positively related to fat intake [78], suggesting that, like GAL, ENK may also mediate the overconsumption of fatty foods. This may not be due to a greater energy density or palatability of the fat diet, since PVN ENK is still stimulated by a high-fat meal when it is equal in caloric density and palatability to a low-fat control meal [78]. Also, mice lacking the ENK gene are less willing to work for food reinforcers than are wild-type mice [79], confirming the role of this peptide in palatable food intake. Interestingly, recent data from our laboratory show that, although GAL and ENK are normally expressed in separate neurons in the PVN, they begin to be co-expressed when animals consume a high-fat diet [80], suggesting that these two peptides may work together to exert their effects on fat intake.

2.1.3. The perifornical lateral hypothalamus—The two major orexigenic peptides within the PFLH are OX, also known as hypocretin, and MCH. Like GAL and ENK in the PVN, these two peptides are expressed in separate neurons in the PFLH [81], but they appear to play opposite roles in some physiological functions, including sleep-wake states [82] and the development of obesity [83]. Believed to coordinate arousal with energy balance [84], OX clearly drives palatable food intake. Expression of OX is strongly upregulated during fasting [18, 85], and hypothalamic injection of OX stimulates food intake [86–88]. Injection of OX-A into the third ventricle adjacent to the hypothalamus specifically stimulates consumption of a high-fat diet in preference to a carbohydrate diet [89], although it can also increase sucrose intake when fat is not also available [90]. In turn, consumption of a high-fat diet compared to a moderate- or low-fat diet for up to two weeks stimulates expression and levels of OX in the PFLH [55, 91, 92], illustrating that OX may also drive the overconsumption of palatable food, particularly fatty food.

Like OX, MCH also drives palatable food intake. Expression and levels of this peptide are increased during fasting [17, 93], and hypothalamic injection of MCH stimulates food intake [94, 95]. This peptide, while capable of driving fat intake, may be more related to palatable food in general. Injection of MCH into the cerebral ventricles stimulates intake of a high-fat diet more strongly than it does chow [96], but it also increases sucrose and glucose intake [97–99]. On the other hand, fat but not saccharin consumption stimulates MCH expression

[100, 101], and transgenic mice that overexpress MCH consume more of a high-fat diet than wild-type mice [102], confirming the relationship of this peptide with dietary fat.

2.2. Mesocorticolimbic neurochemicals and palatable food consumption

2.2.1. The ventral tegmental area—The VTA is the location of the DA-containing neurons that project to limbic areas, such as the NAc and medial PFC (mPFC) [103]. This region receives hypothalamic OX projections, which increase the activity of its DA neurons [104], and it also contains receptors for GAL and ENK [105, 106]. Injections of ENK agonists into the VTA, as they do in the hypothalamus, stimulate food intake [107, 108], likely due to their stimulation of DA cell firing [109]. Further, acute food intake increases the release of DA into the VTA [110], although long-term consumption of a high-fat compared to low-fat diet suppresses expression of tyrosine hydroxylase, suggesting the existence of a complex relationship between mesocorticolimbic DA and palatable food intake.

2.2.2. The nucleus accumbens—The NAc is one of the major recipients of VTA DA, but it also receives acetylcholine (ACh) from a small but important set of interneurons, as well as ENK from its spiny projection neurons [111]. While the precise roles of DA and ACh in the NAc are a matter of ongoing debate (see, for example [112–115]), the Hoebel laboratory has recently proposed a special relationship between these two neurotransmitters in this brain region. They suggest that DA in the NAc fosters approach, while ACh release fosters avoidance and may also counteract excessive DA-mediated approach behavior [116]. With this in mind, it is particularly interesting that hypothalamic injections of GAL or ENK agonists, which stimulate fat intake (see Section 2.1.2.), also raise accumbal levels of DA while decreasing levels of ACh [117, 118].

Support for the theory that NAc DA and ACh can foster approach and avoidance, respectively, is found in feeding studies. Although food-deprived rats show lower than normal DA levels [119, 120], a small rise in accumbal DA, as occurs with local injections of low doses of DA agonists, can stimulate food intake [121, 122]. Further, intake of palatable high-fat or high-carbohydrate foods significantly raises extracellular levels of DA, particularly in the shell region of the NAc [123–126], where drugs of abuse also release DA [113]. These results suggest that low basal levels of DA could induce animals to seek out and consume substances that would raise these levels and that a small rise in DA might be needed immediately prior to a meal in order to induce this behavior. Opposing these actions is ACh. Levels of this neurotransmitter rise during food intake along with DA, but they peak immediately following maximal intake [125, 127], pointing to ACh as mediating satiety. In support of this, cholinotoxic lesions of the NAc lead to increased food intake [128]. Thus, ACh in this region may counteract the actions of DA.

Enkephalin in the NAc appears in some respects to act similarly to DA in this region, likely due to the fact that ENK agonists in the NAc facilitate DA release [129, 130]. Injections of ENK agonists in the NAc increase the preference for a fat over a carbohydrate diet [24] although they also stimulate sucrose and even salt intake when these foods are presented individually [25]. Also, as with the relationship of fat to ENK in the hypothalamus, fat intake further stimulates ENK expression in the NAc [131], pointing to another region where ENK may work in the overconsumption of fatty foods.

2.2.3. The prefrontal cortex—While the PFC also receives VTA DA, the relationship of its neurochemicals with palatable food intake has been less well-described and appears to be different from that seen in the NAc. As with the NAc, DA is released in the mPFC in response to fat or sucrose intake [132, 133], suggesting that extracellular DA may contribute

to this intake, although one recent study found that D1 receptor antagonism in this region did not affect high-fat pellet self-administration [134]. In contrast to the NAc, ACh in the mPFC appears to drive food intake as levels rise during the initial but not later part of a scheduled meal [135]. Also, ENK in the mPFC may in fact be more closely related to carbohydrate than to fat intake. The only study to investigate this found that intra-mPFC infusions of an ENK analogue can selectively increase carbohydrate intake, even in rats that show a baseline preference for fat [136]. While clearly involved in palatable food intake, the mPFC displays a unique role in this process.

3. Regulation of ethanol consumption

The regulation of ethanol consumption was initially believed to be controlled by mesolimbic circuits, such as those modulating synaptic DA levels. However, work pioneered by Bart Hoebel's lab in collaboration with our own has provided evidence to support an additional role for specific hypothalamic peptides in the regulation of ethanol intake. Soon thereafter, it became apparent that consummatory behavior involving fat shares similar neurochemical substrates with that of ethanol.

3.1. Hypothalamic peptides and ethanol consumption

3.1.1. The paraventricular nucleus—Just as with fat ingestion, the peptides GAL and ENK specifically within the PVN display a special relationship with ethanol consumption. Injection studies performed in the Hoebel and Leibowitz labs demonstrate that GAL, when microinjected into the PVN or the adjacent third ventricle can potently stimulate alcohol intake in rats, while injection of a GAL antagonist has the opposite effect of reducing drinking behavior [137, 138]. Further studies by our labs, employing rodent voluntary drinking models, demonstrated that chronic ethanol can also enhance the expression of GAL in the PVN [139], suggesting that, as with fat, GAL shows a positive relationship with ethanol intake that may lead to excess ethanol overconsumption. Further support of this relationship comes from studies in mutant mice, where those lacking the gene coding for GAL consume less ethanol, while those overexpressing this peptide drink more than wild-type mice [74, 140].

The opioid peptide, ENK, can also stimulate ethanol drinking when injected into the PVN, with more potent effects observed with delta-opioid receptor agonists compared to mu-opioid receptor agonists [35]. This is somewhat surprising, given that mu-opioid knockout mice drink less ethanol than wild-type mice [141] and that delta-opioid receptor knockout mice drink more [142]. These contrasting results may be due to differences in opioid receptor function in different regions of the brain, such as the hypothalamus compared to the NAc. Similar to the effects of ethanol consumption on GAL, PVN expression of ENK is also dose-dependently increased by both acute and chronic ethanol exposure [143–145], suggesting that ethanol ingestion itself may regulate peptides within the PVN to further promote the consumption of this rewarding substance [36]. These studies collectively point to a critical role of GAL and ENK, specifically within the hypothalamus, in promoting ethanol consumption in addition to fat ingestion, as previously described (Section 2.1.2.).

3.1.2. The perifornical lateral hypothalamus—Within the PFLH, OX and MCH also regulate ethanol consumption in addition to fat ingestion. In animals trained to consume physiologically relevant amounts of ethanol, Hoebel and colleagues have demonstrated that hypothalamic injection of OX can selectively increase ethanol intake in preference to chow or water [146], and others have demonstrated that peripheral injections of an OX receptor antagonist can reduce drinking behavior [147–149]. The expression of OX is also affected by ethanol consumption. While acute exposure to ethanol dose-dependently enhances OX

expression, chronic ingestion of this substance reduces its expression and levels [150]. This may be due, in part, to inhibitory feedback mechanisms that become activated in response to long-term ethanol use. Thus, through its positive feedback with ethanol in the short-term, OX may be more important in the early stages of drinking rather than later stages.

The MCH peptide interacts with ethanol in much the same way as OX. Hypothalamic and third ventricular injection of MCH stimulate ethanol drinking [37, 98], while systemic MCH receptor antagonists reduce it [151]. This peptide similarly increases ethanol intake when injected into the NAc [37], suggesting that MCH also acts via distant reward centers to promote excessive ethanol intake. Like OX, acute ethanol enhances MCH expression, while chronic ethanol drinking suppresses it [37]. Thus, these hypothalamic peptides, which show a special relationship with dietary fat, also play a role in driving ethanol intake.

3.1.3. The arcuate nucleus—In contrast to the peptides within the PVN and PFLH, NPY within the ARC largely appears not to drive ethanol intake. Central injections of NPY into the hypothalamus or cerebral ventricles have been found to suppress [152, 153] or have no effect [153, 154] on ethanol drinking. The expression of this peptide is also reduced by both acute and chronic ethanol exposure [139, 155, 156]. These effects may be due to the stronger relationship of NPY to carbohydrates than to fat. The ingestion of ethanol, a calorie-containing substance, may be perceived as a positive energy state and thus reduce the expression of this feeding peptide. In further support of this inverse relationship with ethanol, mice lacking the gene encoding NPY show enhanced ethanol intake, while those that overexpress NPY show reduced drinking [157]. These studies collectively suggest that NPY, a peptide primarily expressed in the ARC and related to carbohydrate ingestion, is inversely related to ethanol consumption.

3.2. Mesocorticolimbic neurochemicals and ethanol consumption

3.2.1. The ventral tegmental area—Outside of the hypothalamus, just as with food intake, ethanol stimulates DA neuron firing in the VTA [158, 159], mediating the rewarding aspects of ethanol consumption. While injection of DA agonists into the VTA suppresses ethanol intake [160, 161], this appears to be due to stimulation of D2 autoreceptors in this region that would decrease DA release. Ethanol intake can also stimulate ACh release in the VTA, which occurs in parallel with an increase in DA levels in the NAc [162]. In contrast to its role in the NAc, ACh in the VTA, through nicotinic receptors on DA neurons [163], can promote firing of VTA DA neurons and release of DA in terminal regions [162, 164]. In turn, ACh in the VTA may drive further ethanol intake, as injection of cholinergic antagonists into the VTA decreases ethanol self-administration [165]. Thus, in the VTA, ethanol stimulates DA neurons, which can then lead to further ethanol intake.

3.2.2. The nucleus accumbens—Perhaps the most well characterized response to ethanol consumption is the release of DA into the NAc [166, 167]. This release may prolong drinking once it has begun, as DA agonists injected into the NAc generally increase ethanol self-administration [168, 169] while antagonists decrease it [170]. Further, D1 receptor knockout mice show markedly less preference for ethanol than wild-type mice [171], supporting the role of DA in promoting ethanol intake.

Although ethanol is not found to significantly affect extracellular levels of ACh in the NAc, withdrawal from ethanol results in increased ACh levels [138], and accumbal ACh neurons become more sensitive to stimulation several weeks after long-term ethanol intake [172, 173]. Thus, in accord with Hoebel's theory on the role of accumbal ACh, this increase in ACh may mediate the aversiveness of ethanol withdrawal [116]. Interestingly, injection of both ACh agonists and antagonists into the NAc has been shown to reduce ethanol self-

administration [174], indicating that the relationship of accumbal ACh with ethanol is complex and may be indirect. It appears that ACh may have a stronger role in influencing ethanol drinking behavior through its actions in the VTA.

Aside from DA and ACh, ENK in the NAc also plays a role in ethanol consumption. Acute ethanol stimulates the release of met-ENK into the NAc [175, 176], and chronic ethanol drinking has been reported to stimulate ENK expression in this region [143], although other studies have found no change [177] or a decrease in ENK [145, 178]. In turn, microinjection of ENK agonists into the NAc has been found to increase ethanol drinking in rats, while antagonists block such behavior [25, 179]. Further, alcohol-preferring mice have increased NAc ENK expression compared to alcohol-avoiding mice [180]. Collectively, these studies suggest that DA, ENK and ACh in the NAc, as with fatty food, may all play a role in promoting ethanol consumption.

3.2.3. The prefrontal cortex—In the mPFC, just as with palatable food intake, ethanol stimulates the release of DA [181, 182], although both a D2/3 agonist and D2 antagonist are found to reduce ethanol self-administration [183]. Ethanol also stimulates ACh release, although this occurs in a biphasic manner, with low doses increasing and high or chronic doses decreasing its release in the mPFC [184, 185]. It also increases ENK expression in the mPFC [143, 186]. At this time, the effect of ACh and ENK in the PFC on ethanol intake remains to be determined.

4. Lipids as possible mediators of similarities between ethanol and fat

4.1. Behavioral relationship of fat and ethanol

Much as fat and ethanol intake individually demonstrate elements of positive feedback, behavioral studies conducted in the Hoebel and Leibowitz labs, among others, also demonstrate a close relationship between fat and ethanol intake. Rats maintained on a high-fat diet or exhibiting a preference for fat are found to consume more ethanol [187, 188]. Similarly, injection of ethanol preferentially stimulates consumption of fat relative to carbohydrate [189]. Clinical studies show that fat intake is elevated in ethanol drinkers, with bingeing on fat-rich foods associated with high rates of alcoholism [190, 191], and drinkers on a fat-rich diet compared to carbohydrate-rich diet exhibiting shorter periods of abstinence from ethanol [192, 193]. Thus fat and ethanol, possibly through their similar effects on specific neurochemicals, may substitute for one another in the positive feedback that leads to escalating intake.

4.2. Relationship of fat and ethanol with lipids

The behavioral relationship between fat and ethanol and their similar relationships with specific neurochemicals may involve lipids, specifically triglycerides (TG) and their component fatty acids (FAs). Dietary fat raises circulating levels of TG in direct proportion to the amount consumed [65, 194, 195]. This effect is evident under chronic feeding conditions, with hypertriglyceridemia a common trait in animals and humans overeating a fat-rich diet, and it is also seen in acute feeding paradigms, with TG levels rising higher and remaining elevated for longer periods after fat-rich meals. Similarly, acute and chronic ethanol raises circulating TG levels [144], and hypertriglyceridemia is also seen in human alcoholics [196, 197]. Notably, the consumption of dietary fat and ethanol together produces a considerably larger increase in TG than intake of a fat-rich diet alone or of ethanol with a low-fat diet [189], pointing to a synergistic effect from their intake. In support of the idea that lipids mediate the positive feedback of fat or ethanol intake, there is evidence that ethanol consumption is stimulated by injection with the lipid emulsion Intralipid, which

increases TG and FA levels [187, 198], and it is reduced by the fibrate drug, gemfibrozil, which lowers TG levels [189].

4.3. Relationship of lipids with peptides related to fat and ethanol

The increased lipid levels caused by fat and ethanol intake may be responsible for the changes in neurochemicals that also occur with their intake. After a small high fat meal, rats that exhibit higher levels of circulating TGs also have higher hypothalamic expression of ENK, OX and MCH than those with lower TGs [199]. Similarly, Intralipid, which increases TG and FA levels, also increases hypothalamic expression of GAL, ENK and OX [198]. In contrast, there is evidence that FAs may not affect or even inhibit NPY expression, with rats injected with Intralipid compared to saline showing no change in NPY [198] and mutant mice with lower levels of hypothalamic FAs showing increased NPY compared to wild-type mice [200]. Further, lowering TG levels with gemfibrozil, which reduces subsequent ethanol drinking, also decreases OX expression prior to this behavioral outcome [189]. Beyond the hypothalamic peptides, lipid levels may also be responsible for the increase in DA that occurs with and possibly further drives fat and ethanol intake. Dietary fatty acid deficiency leads to decreased DA release in both the NAc and PFC [201], while injection of Intralipid increases DA release in the NAc [202]. Whereas the precise FAs that mediate these effects remain to be determined, it is clear that lipids are a major candidate for explaining the similarities between fat and ethanol intake.

5. Disturbances in animals prone to overconsumption of palatable food or ethanol

In the last few years, researchers have begun to ask if neurochemicals that are affected by consumption of palatable food or ethanol might already be dysregulated in animals prone to overconsuming these substances. Therefore, it has become important to study these prone animals without the confounding effects of substance exposure and also to develop ways to identify these animals. We and others have recently established several methods for identifying these prone animals and have found that rats prone to fat or ethanol overconsumption over the long term can be identified using specific behavioral or biomarkers and that these prone animals already show significant neurochemical disturbances that also occur in association with fat or ethanol intake.

5.1. Behaviors that predict palatable food or ethanol intake

Using outbred rats, several tests have been developed that identify animals prone to consuming higher amounts of fat or ethanol. These include early intake, fat-induced TG, and novelty-induced locomotor activity. Early intake builds on the idea that patterns of intake during initial access to a substance hold constant relative to other animals. Similar to our model with Sprague-Dawley rats that identified obesity-prone animals based on their higher weight gain during initial access to a high-fat diet [203], we can now identify animals prone to overconsuming a high-fat diet based on their higher intake during few days of access to this diet, as they continue to eat approximately 35% more calories than control animals when maintained on this diet for several weeks or when later re-exposed to the diet [131]. Similarly, we and others have found that ethanol intake during the first few days of exposure identifies the rats that will consume up to three times more ethanol than other rats during later stages of continuous training or during re-exposure [204, 205]. Thus, the amount of 2% ethanol a rat drinks over a few days predicts how much 9% ethanol it will drink later during several weeks of access.

Our model of fat-induced TG builds on the idea that lipids stimulate the peptides that, in turn, drive fat and ethanol intake. We have found that rats given a small high-fat meal (15

kcal) exhibit a wide range of TG levels that remain relatively constant from day to day. Remarkably, we have also found that those rats having the highest TG, in addition to going on to eat more of a high-fat diet during a three-week exposure [199], also go on to drink more 9% ethanol during a three-week access [204].

The model of novelty-induced locomotor activity builds on the idea that some animals overconsume palatable food or drugs of abuse due to the trait of sensation-seeking. This model examines relative locomotor activity during just a few minutes in a novel open field. Rats that exhibit higher levels of novelty-induced locomotor activity, spending more time exploring this new environment, go on to eat more of a high-fat diet [206], drink more 9% ethanol or exhibit more lever-pressing for ethanol [204, 207], and show greater preference for a sucrose solution [208].

5.2. Neurochemical disturbances in predicted overconsumers

The application of these tests to identify animals prone to overconsuming palatable food or ethanol has begun to point to neurochemical differences that may drive this overconsumption. Remarkably, we and others have found that some of the same neurochemicals that respond to and drive both fat and ethanol intake are already endogenously disturbed in predicted overconsumers with little or no exposure to these substances. Within the PVN, GAL expression is higher in predicted overconsumers immediately after their initial exposure to ethanol or a fat-rich meal [204]. Additionally, ENK is higher in predicted overconsumers using all three of the above tests. Expression of this peptide is elevated in rats that show higher initial intake of fat or ethanol [131, 204], greater levels of TG after a high-fat meal [199, 204], and higher locomotor activity in a novel open field [204]. Thus far, these findings with ENK and GAL have largely been in rats immediately after the application of these predictor tests, so changes induced by the testing itself cannot be excluded. However, high-fat consumers identified by their initial intake and then subsequently maintained for several weeks on lab chow also show increased ENK in the PVN as well as the NAc, while selectively-bred alcohol-preferring rats and mice exhibit increased ENK expression in both the NAc and PFC [180, 209].

Peptides within the PFLH may also be disturbed in predicted overconsumers. High-fat consumers identified by their initial fat intake and then maintained on chow have higher expression of both OX and MCH compared to animals that normally regulate their fat intake [206]. Overconsumers identified by higher TG after a high-fat meal also have greater expression and levels of these peptides compared to animals with lower TG [199]. In contrast, NPY in the ARC may not be disturbed prior to fat or ethanol intake. Immediately after testing, this peptide is elevated only in animals with higher novelty-induced locomotor activity, but not in animals with higher 2% ethanol drinking or fat-induced TG [204]. The findings thus far suggest that rats prone to fat or ethanol consumption have inherently higher expression of the specific peptides known through injection and genetic studies to stimulate this intake.

In contrast to the hypothalamic peptides, mesocorticolimbic DA appears to actually be lower in animals prone to overconsumption. Recently, Pothos and colleagues found that inbred obesity-prone rats have lower levels of extracellular NAc DA and attenuated DA release after stimulation in the NAc and mPFC compared to obesity-resistant rats [210]. Similarly, in collaboration with the Hoebel lab, we have found that obesity-prone rats with a tendency to overconsume fat but maintained on chow also have lower NAc DA levels [202]. In further support of the idea that low DA predisposes animals toward overconsumption, this has also been found in rats with greater novelty-induced locomotor activity [211], as well as in several selectively-bred alcohol-preferring rat lines [212–214]. It seems likely that rats

consume higher levels of palatable food or ethanol, which increase levels of accumbal DA [124, 125, 215], in order to return DA back to normal levels.

6. Conclusions

As research on ingestive behavior has progressed, it has uncovered more and more similarities between the regulation of palatable food intake and drug intake. Studies of food intake regulation started with the hypothalamus and gradually expanded to mesocorticolimbic regions, identifying specific neurochemicals particularly related to fat or sucrose intake. In contrast, studies of drug use began with mesocorticolimbic regions and now include the hypothalamus. Interestingly, as proposed by the Hoebel laboratory in collaboration with our own, the same neurochemicals involved in promoting fat intake also promote ethanol intake. These include the hypothalamic peptides GAL, ENK, OX and MCH as well as the mesocorticolimbic neurochemicals DA and ACh. These hypothalamic peptides in particular show a positive feedback relationship with fat and ethanol, being stimulated by their intake and themselves further stimulating their intake. In contrast, NPY, which promotes carbohydrate intake, is unrelated to or inhibits fat and ethanol intake. The positive relationship of specific neurochemicals with fat and ethanol intake is likely driven by circulating lipids, which are stimulated by fat and ethanol intake, known to increase expression and levels of the neurochemicals, and also promote fat and ethanol intake. Most recently, we and others have worked to develop methods for predicting which rats are likely to go on to consume higher levels of fat or ethanol. Not only do these tests work equally well for identifying rats prone to fat or ethanol overconsumption but, remarkably, they suggest that these animals already show disturbances in these neurochemicals prior to substance exposure. Thus, endogenously higher GAL, ENK, OX and MCH and lower mesocorticolimbic DA may make certain individuals more likely to use and overconsume fat or ethanol. This body of research, influenced in large part by Bart Hoebel's work over several decades, should ultimately allow clinicians to more effectively treat and even prevent the growing incidence of eating and alcohol use disorders in a society where fat-rich foods as well as alcoholic drinks are so abundantly available.

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Research Highlights

- Research on fat and alcohol intake has converged on similar brain areas
- Specific neurochemicals drive fat intake through positive feedback
- Many neurochemicals involved in fat intake are also involved in ethanol intake
- Similarities between fat and ethanol may be mediated by circulating lipids
- Fat and ethanol neurochemicals may already be disturbed in predicted overconsumers

Figure 1.

Research on food and ethanol intake progressed from different brain regions and neurochemicals but ultimately converged. Abbreviations: ACh, acetylcholine; ARC, arcuate nucleus; DA, dopamine; ENK, enkephalin; GAL, galanin; MCH, melanin-concentrating hormone; ME, median eminence; NAc, nucleus accumbens; NPY, neuropeptide Y; OX, orexin; PFC, prefrontal cortex; PFLH, perifornical lateral hypothalamus; PVN, paraventricular nucleus of the hypothalamus; VTA, ventral tegmental area.

Figure 2. Schematic representation of neural connections and neurotransmitter content of some principal nuclei that promote overconsumption. See legend of Figure 1 for abbreviations. Rat brain image adapted from Paxinos and Watson [216].