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Regulation of Drug and Palatable Food Overconsumption by Similar Peptide Systems

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Abstract

This review is aimed at understanding some of the common neurochemical, behavioral and physiological determinants of drug and food overconsumption. Much current work has been devoted to determining the similarities between the brain circuits controlling excessive use of addictive drugs and the overconsumption of palatable foods. The brain systems involved likely include peptides of both mesolimbic and hypothalamic origin. Evidence gathered from expression and injection studies suggests that the consumption of drugs, such as ethanol and nicotine, and also of palatable foods rich in fat is stimulated by different orexigenic peptides, such as enkephalin, galanin, orexin, and melanin-concentrating hormone, acting within the hypothalamus or various limbic structures, while another peptide, neuropeptide Y, is closely related to carbohydrate consumption and shows an inverse relationship with ethanol and nicotine consumption. Moreover, studies in animal models suggest that a propensity to overconsume these reinforcing substances may result from preexisting disturbances in these same peptide systems. These neurochemical disturbances, in turn, may also be closely linked to specific behaviors associated with excessive consummatory behavior, such as hyperactivity or novelty-seeking, palatable food preference, and also fluctuations in circulating lipid levels. Clear understanding of the relationship between these various determinants of consummatory behavior will allow researchers to effectively predict and examine at early stages of exposure animals that are prone to drug and food overconsumption. This work may ultimately aid in the identification of inherent traits that increase the risk for drug abuse and palatable food overconsumption.

Keywords

Ethanol; fat; hypothalamus; mesolimbic; nicotine; peptides

I. INTRODUCTION

The overconsumption of drugs such as ethanol and nicotine and also of palatable foods rich in fat or sugar may be driven by common underlying neurobiological, behavioral and physiological mechanisms. Recent clinical as well as preclinical research has focused attention on understanding the similarities in the brain circuitry involved in the consumption of these various substances, with mesolimbic and hypothalamic regions being particularly

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important in mediating such behavior [1–4]. The mesolimbic pathway, which includes the nucleus accumbens (NAc) and ventral tegmental area (VTA), is perhaps the best known for its role in reward and reinforcement [5]. Within this pathway, the release of the neurotransmitter, dopamine, is found to be closely related to the reinforcing effects of commonly abused drugs, such as ethanol and nicotine [6], and, more recently, of palatable foods, such as those rich in fat [7, 8] or sucrose [9, 10]. Within this circuit, there are other neurochemicals, such as the opioid, enkephalin (ENK), which can interact directly with dopamine to alter its neurotransmission and release [11, 12]. In addition to the mesolimbic system that is closely related to substance reinforcement, there are energy-sensing neurochemicals in the hypothalamus that promote the overconsumption of these substances. Within the hypothalamus, the orexigenic peptides include orexin (OX), also known as hypocretin, and melanin-concentrating hormone (MCH) that are expressed by neurons in the perifornical lateral hypothalamus (PFLH) [13–15]; galanin (GAL) and ENK that are expressed in the paraventricular nucleus (PVN) [16, 17]; and also neuropeptide Y (NPY) that is expressed predominantly in the arcuate nucleus (ARC) [18]. With peptides in the ARC strongly linked to the control of energy balance and caloric intake [19, 20] and the PFLH and PVN more closely related to the consumption specifically of dietary fat [2, 19, 21], these energy-sensing circuits within the hypothalamus have recently been shown to play an additional role in the consumption of certain drugs, such as ethanol and also nicotine, possibly by directly interacting with distal mesolimbic regions including the NAc and VTA [2, 22–26].

Consummatory behavior as it relates to both drugs and food may also be driven by various behavioral disturbances, related to locomotor activity, novelty-seeking, anxiety, or sweet preference, and perhaps even physiological factors, such as circulating lipids. For example, animals that are more active in novel situations or that consume greater amounts of a sweet saccharin solution are ultimately found to become high consumers of either drugs or palatable food [27–32]. Moreover, these behaviors themselves are closely associated with unique patterns of mesolimbic or hypothalamic peptide expression. Thus, with specific neurochemicals driving drug and palatable food intake along with behaviors related to anxiety, activity and reward responding, it is possible that animals prone to excessive intake will show altered neurochemical activity even prior to exposure to these substances.

Different rodent models, such as genetically altered mice, selectively bred or inbred rats, and behaviorally distinct outbred rats, provide useful tools for studying common neurochemical, behavioral and physiological factors contributing to drug and food overconsumption. Examining these various models prior to any exposure to the drug or food substance itself is especially important as it may yield significant information regarding the factors causally related to the future consummatory behavior. In the current review, we will summarize evidence collected in such models to demonstrate how animals that are prone to overconsuming ethanol, nicotine or palatable food can be identified by specific patterns of mesolimbic and hypothalamic peptide expression along with disturbances in specific behaviors as well as circulating lipid levels.

II. DRUG OVERCONSUMPTION

Two commonly abused drugs, ethanol and nicotine, may be consumed in excess due to their ability to act on peptide systems within the mesolimbic and hypothalamic circuits. These peptides include ENK, GAL, OX, MCH and NPY, which function to regulate drug intake, in addition to food consumption as discussed in subsequent sections. The intake of ethanol and nicotine can also be promoted by affective behaviors related to consumption, which may also be driven by disturbances in these same peptide systems. The goal of the next few sections is to describe how animals prone to drug overconsumption, prior to drug exposure, can be identified by their distinct patterns of peptide expression, behavioral traits and physiological factors.

Peptide Regulation of Ethanol Intake

The opioid peptide, ENK, has been shown to control ethanol consumption and reinforcement by acting within mesolimbic regions, such as the VTA and NAc, and also the hypothalamic PVN. Injection studies in rats have clearly demonstrated a stimulation of ethanol consumption with administration of specific ENK analogous in the NAc [22, 33, 34] and PVN [35] and also in the VTA where mu- and delta-specific opioid agonists produce signs of place preference [36, 37] but the kappa agonist causes place aversion while reducing ethanol intake [36, 38]. Endogenous expression of ENK in the NAc [39–41] and PVN [42, 43] is also stimulated by acute and chronic exposure to ethanol, suggesting that ethanol itself can activate this peptide system, which in turn functions to further promote consummatory behavior. Similar to ENK in the PVN, the peptide GAL in this region also stimulates ethanol drinking behavior in rats [24, 44], and its expression in the PVN is enhanced by the consumption of ethanol solution [45]. These studies suggest that a positive feedback loop, involving ENK in the NAc and PVN and also GAL in the PVN, may contribute to the overconsumption of ethanol.

Evidence suggests that the peptides OX and MCH, expressed primarily in the PFLH, also play a major role in ethanol consumption. Injection of OX into the PFLH can enhance the drinking of ethanol [24], and peripheral injection of specific OX receptor antagonists reduces both responding and preference for ethanol [46–48]. The peptide MCH, when injected into specific subregions of the PFLH, the NAc or the third cerebral ventricle, also stimulates ethanol drinking in rats, with the most potent effect occurring in the lateral hypothalamus and NAc [23, 49]. Expression of both OX and MCH is also increased by acute oral administration of ethanol but not chronic ethanol [23, 46, 50], suggesting that these PFLH peptides may promote drinking behavior more during the initial stages of ethanol consumption than subsequently during repeated episodes of chronic drinking. In contrast to the circuits mentioned above, the peptide NPY, which is primarily expressed within the ARC, functions to reduce ethanol consumption. In ethanol-preferring animals, central injection of this peptide into the cerebral ventricle or PVN, a specific target projection area, has been shown to reduce ethanol consumption [51, 52]. Also, in contrast to the other peptides, NPY expression in the ARC is reduced by both acute and chronic ethanol intake [45, 53, 54]. This evidence suggests that, while peptides expressed in the PVN and PFLH

may positively regulate ethanol consumption, those in the ARC provide a negative control to limit such behavior.

With this evidence demonstrating how mesolimbic and specific hypothalamic peptides can function to stimulate ethanol consumption while also responding positively to the consumption of this substance, it is likely that disturbances in these systems in various animal models may lead to the overconsumption of ethanol.

Peptide Disturbances in Relation to Ethanol Overconsumption

Animal models of ethanol overconsumption, such as genetically modified or inbred mice or selectively bred rats, exhibit disturbances in several orexigenic peptides known to promote ethanol intake. For example, although ENK knockout mice fail to show disturbances in ethanol responding or preference [55, 56], mice lacking the mu opioid receptor gene demonstrate a reduction in ethanol intake [57], supporting a role for this opioid receptor in controlling the consumption of ethanol. Whereas studies of ENK in ethanol-preferring compared to non-preferring rats have yielded mixed results showing increased [58] as well as reduced [59–61] expression in different limbic regions, the specific opioid receptors, mu and delta, in the NAc are consistently found to be increased in ethanol-preferring rodents under ethanol-naïve conditions [62–64]. The overexpression of GAL is also associated with an increase in drinking behavior in rats [65], while deletion of the GAL gene in mice results in a significant reduction in ethanol intake compared to wild-type (WT) animals [66]. Although the expression of GAL in selectively-bred, ethanol-preferring rodents has yet to be studied, mutations in the genes encoding GAL or the GAL 3 receptor have been associated with clinical alcoholism [67, 68]. These animal and human studies suggest that specific disturbances in ENK and GAL, prior to any ethanol exposure, may drive animals to consume increased amounts of ethanol.

Although the peptides OX and MCH in the PFLH are believed to play a significant role in ethanol overconsumption, their expression has yet to be systematically examined in inbred or selectively-bred ethanol-preferring animals, with one study showing no change in OX mRNA in ethanol-preferring rats [46]. Also, with regard to MCH, mice lacking the MCH receptor are found to consume increased amounts of an ethanol solution, suggesting that this peptide’s relationship to ethanol may be complex [69]. The negative relationship of NPY with ethanol intake, as described above, is further supported by studies in mutant mice, showing exaggerated ethanol intake in mice lacking the NPY or NPY receptor gene [70, 71] and reduced ethanol intake in mice overexpressing NPY [71]. It is also evident in several ethanol-preferring rat and mouse models, which exhibit reduced NPY immunoreactivity in the ARC and PVN and also reduced NPY expression in the amygdala [72, 73]. Thus, although mixed results have been obtained for OX and MCH in the PFLH of ethanol overconsuming animals, the evidence for NPY seems clear in suggesting an inverse relationship of this peptide to ethanol preference and intake.

Behavioral Disturbances in Relation to Ethanol Overconsumption

Behaviors such as locomotor activity, novelty- seeking, anxiety and preference or intake of sweet substances are found to be positively associated with ethanol consumption, although

the strength of their relationship can vary. For example, increased locomotor activity has been reported in ethanol-preferring compared to non-preferring rats [74], and it has also been shown to predict ethanol intake in several non-preferring rat strains [75, 76]. The predictive value of locomotor behavior largely depends on the session duration or acclimation to the test chambers, with activity during longer periods or after several exposures to the chamber showing little association with subsequent ethanol consumption [76, 77]. An increase in novelty-induced locomotor activity has also been reported specifically in ethanol-preferring rats [32], although contradictory results have been obtained in outbred rats prior to ethanol access [77–79]. Anxiety also seems to be a weak predictor of ethanol consumption, with several studies showing preferring rats to be more anxious than their non-preferring counterparts [80, 81] but others failing to demonstrate this in certain rat strains [82–84]. Perhaps the strongest predictor of future ethanol consumption is the tendency to consume increased amounts of sweet substances, such as saccharin or sucrose. Increased ethanol intake has been reported in rats selectively bred for high versus low saccharin consumption [29] and also in outbred rats that tend to consume greater amounts of saccharin [29, 85, 86]. Similarly, increased self-administration of a sucrose solution is strongly and positively correlated with the initial consumption of ethanol [87]. Further support for this positive relationship comes from evidence suggesting that rats selectively bred to consume more ethanol also consume more sucrose [88]. These studies indicate that, while locomotor activity, novelty-seeking and anxiety have some limited value in predicting ethanol consumption, the intake of sweet substances is consistently shown to be the strongest marker of this consummatory behavior.

Peptide Disturbances and Behavioral Predictors to Ethanol Overconsumption

Behaviors that promote ethanol consumption, such as activity, novelty-seeking, anxiety and sweet preference/consumption, are also linked to disturbances in orexigenic peptide expression. Indeed, rats exhibiting increased novelty-induced locomotor behavior also exhibit higher levels of ENK mRNA in the PVN but not in other limbic regions [79, 89], suggesting that ENK specifically in the hypothalamus may be a determinant of high novelty-related activity in addition to ethanol overconsumption. Data from mutant mice further suggest that the expression of OX or GAL is positively associated with increased locomotor behavior [90, 91], while NPY shows both a direct [70, 92] and inverse relationship [93] with this behavior. Studies of anxiety show this behavior to be positively related to MCH and NPY but inversely related to ENK and GAL. Mutant mice lacking the ENK gene exhibit high anxiety-related behavior [94–96], while inbred animals of high anxiety show reduced ENK expression in the prefrontal cortex and striatum [97], and animals lacking the GAL 2 receptor show exaggerated stress responding [98, 99], while those showing high anxiety have reduced levels of hypothalamic GAL mRNA [100]. In contrast to ENK and GAL, anxiety seems to be directly related to MCH and NPY, with studies showing a clear reduction in various measures of such behavior in mice lacking MCH [101, 102] and specific NPY receptor subtypes [103] and greater anxiety in animals overexpressing NPY [104]. With consumption of sweet substances being the strongest predictor of future ethanol consumption, it is interesting to note that, while mutations of the GAL [66], ENK [105] or NPY [70, 106] systems have little effect on sucrose preference, mice lacking OX exhibit a strong reduction in sucrose intake [91]. Although more work in specific animal strains and

selectively bred rats is needed to fully understand how disturbances in these various behaviors may be a function of inherent peptide differences, the studies reviewed here provide initial evidence to suggest a close relationship among these behaviors and peptides that ultimately drive ethanol consumption. Specifically, a consistent, positive relationship is evident between hypothalamic ENK and novelty-related behaviors, between both OX and GAL and locomotor activity, and both MCH and NPY and anxiety, with OX additionally related to sucrose consumption.

Physiological Disturbances in Relation to Ethanol Overconsumption

There is also evidence that ethanol consumption in outbred rats is closely related to circulating lipid levels. Measurements of serum triglycerides (TGs) after a small fat-rich meal can accurately predict increased ethanol drinking behavior [79]. Moreover, animals that show high levels of fat-induced TGs to also exhibit increased expression of OX and MCH in the PFLH [107] and also of ENK and GAL in the PVN [79, 107], with no difference in NPY expression evident in the ARC [79]. This preliminary, yet promising evidence suggests that fluctuations in lipid levels are related to patterns of ethanol consumption and also peptide disturbances characteristic of ethanol overconsumers.

Peptide Regulation of Nicotine Intake

Recently, much attention has focused on understanding the neurobiological substrates of nicotine abuse, with current investigations pointing to several common circuits regulating the intake of this drug and ethanol. Similar to ethanol, the consumption of nicotine seems to be positively regulated by mesolimbic and hypothalamic ENK as well as OX in the PFLH, with less information on its regulation by GAL or NPY. Acute stimulation by nicotine consistently increases the opioid peptide, ENK, in the hypothalamic PVN and also limbic regions such as the NAc and central nucleus of the amygdala [108–110], whereas chronic nicotine exposure results in either reduced or unchanged expression of ENK in these regions, possibly due to the onset of tolerance [109, 111, 112]. This peptide itself can regulate nicotine consumption, with studies using general or mu-specific opioid antagonists showing a reduction in self-administration behavior [113, 114]. The peptide, OX, can also positively control nicotine consumption, with both acute and chronic nicotine exposure stimulating neurons expressing this peptide as well as peptide levels [115–117]. This positive relationship is further supported by evidence showing cerebroventricular injection of OX-A to increase nicotine-seeking behavior [117] and of OX receptor antagonists to produce a potent and consistent reduction in nicotine self-administration [118, 119]. While no evidence for the role of GAL in nicotine consumption exists, NPY in the ARC and PVN is reduced by acute nicotine exposure [120] and either stimulated or reduced by chronic treatment with this drug [120, 121]. As with ethanol intake, these studies suggest that ENK and OX function to provide a positive control over nicotine consumption, whereas NPY is inversely related to this drug..

Behavioral and Physiological Disturbances in Relation to Nicotine Overconsumption

Similar to ethanol, the overconsumption of nicotine is found to be predicted, to varying degrees, by different behaviors, such as activity and novelty-seeking in addition to ethanol preference itself. In a recent study, mice demonstrating increased locomotor and exploratory

behaviors were characterized as being high consumers of nicotine [30]. Also, novelty-seeking can successfully predict nicotine intake, whereas anxiety appears to be only a weak predictor [122]. Whereas there are no reports of nicotine intake as it relates to an animals' preference for sweet substances, rats that are selectively bred to prefer ethanol are found to self-administer higher amount of nicotine compared to their non-preferring counterparts [31]. These studies, although few in number, provide some evidence that high locomotor activity, novelty-seeking and ethanol preference can identify animals that go on to consume high amounts of nicotine.

As discussed in a previous section, these predictive behaviors are also associated with disturbances in mesolimbic and hypothalamic peptide systems. These include enhanced expression of hypothalamic ENK and OX, which may control locomotor and novelty-related behaviors [79, 91]. These results indicate that animals predicted to consume high amounts of nicotine may have inherent disturbances in the same peptide systems and associated behaviors also linked to high ethanol consumption. Along with these peptide and behavioral characteristics, there is a physiological factor, circulating lipids, which has been linked to increased consumption of nicotine. The administration of nicotine, as with ethanol, has been positively related to high levels of TG and free fatty acids [123, 124]. Since these lipid molecules at high levels are found to be associated with elevated expression of hypothalamic OX, ENK and MCH [107, 125], these physiological variables may also act as valuable predictors of nicotine overconsumption resulting from such peptide disturbances.

III. PALATABLE FOOD OVERCONSUMPTION

Palatable foods include those made with the dietary macronutrients fat and carbohydrate, often sucrose. Both high-fat and high-carbohydrate foods are commonly overconsumed. With fat, this may be due to its caloric density and texture and also to its lesser satiety induction compared to other macronutrients such as protein or carbohydrate [126]. 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 [127–129]. High-carbohydrate foods are also calorically dense, and it is sweet, high-fat foods that are most often consumed during binge eating [130]. Certain neurochemical systems, particularly those in the hypothalamus and mesolimbic areas, have been associated with palatable food overconsumption. It is important to understand how inherent disturbances in these systems, along with behavioral and physiological factors, can drive the overconsumption of palatable foods in various animal models.

Peptide Regulation of Palatable Food Consumption

Similar to drugs of abuse, a number of mesolimbic and hypothalamic peptides have been found to play a role in driving the overconsumption of palatable foods. These include ENK in certain limbic regions, GAL and ENK in the PVN, OX and MCH in the PFLH, and NPY in the ARC. Central administration of ENK agonists into a wide number of regions, including not just the hypothalamus [131] but also the VTA [132, 133], NAc [134], and other mesolimbic regions such as the amygdala and prefrontal cortex [135, 136], can stimulate food intake. Injections into the PVN, NAc or amygdala also specifically increase

fat intake [137–139], although those in the accumbens additionally stimulate sucrose and even salt intake when these foods are presented alone [34]. Recently, injection of ENK analogues in the prefrontal cortex has been shown to selectively increase carbohydrate intake, even in rats with a baseline preference for fat [136]. Within both the hypothalamus and accumbens, however, expression and levels of ENK are positively related to fat intake [27, 125], suggesting that ENK can drive the overconsumption of this diet, similar to drugs of abuse, through actions within hypothalamus as well as nuclei outside of this structure. Like ENK, injection of GAL into the hypothalamus or amygdala stimulates food intake [140, 141]. Injection into the PVN or adjacent third ventricle leads rats to consume a high-fat diet more than a low-fat diet [142, 143], and gene expression and peptide production of GAL in the PVN is also stimulated by consumption of dietary fat but not by carbohydrate or protein [144, 145]. These results suggest that GAL acts primarily through the hypothalamus to drive the overconsumption of fatty foods, just as it does with ethanol.

The peptide OX is believed to coordinate arousal with energy balance [146]. Expression of this peptide is upregulated during fasting [15, 147], and both hypothalamic and accumbal injections of OX stimulate food intake [148–151], suggesting that this peptide functions locally within the hypothalamus and also through projection areas to drive feeding behavior. Injection of OX, specifically OX-A, into the third ventricle stimulates consumption of a high-fat diet in preference to a carbohydrate diet [152]. In turn, consumption of a high-fat diet compared to a moderate- or low-fat diet, or acute administration of fats, stimulates expression and levels of OX in the PFLH [128, 153, 154]. On the other hand, increases in glucose levels, as would occur with sucrose intake, do not affect OX expression or levels [147, 155]. Thus, while OX can drive overconsumption of palatable food in general, it appears to be more closely related to fatty food and shows a positive feedback relationship with this macronutrient. Like OX, expression and levels of MCH are increased during fasting [156, 157], and both hypothalamic and accumbal injections of MCH stimulate food intake [158, 159]. Unlike OX, MCH may be equally related to fat and carbohydrate overconsumption. Injection of MCH into the cerebral ventricles stimulates intake of a high-fat diet more strongly than it does chow [160], but it also increases intake of both sucrose and glucose [49, 161, 162]. This peptide also shows positive feedback with fat, as consumption of a high-fat diet itself stimulates MCH expression [163]. Thus, this peptide, similar to OX, can drive the overconsumption of palatable foods.

Within the ARC, NPY is clearly related to carbohydrate intake. Expression and levels of this peptide rise immediately prior to scheduled feeding as well as during food deprivation [164, 165], and hypothalamic injection of NPY potently stimulates food intake [166, 167]. When given a choice between diets with different macronutrient content, rats injected with NPY increase their ingestion of carbohydrate rather than fat [166, 168]. While the immediate effects (within minutes) of carbohydrate intake may be to decrease hypothalamic NPY expression, likely due to elevated glucose levels [169, 170], chronic carbohydrate intake ultimately results in higher NPY over the long term [171, 172]. Thus, this peptide appears to be important in the overconsumption of foods high in carbohydrates such as sucrose.

Peptide Disturbances in Relation to Palatable Food Overconsumption

Studies examining mutant mice support a role for the different orexigenic peptides in palatable food overconsumption. Mice lacking the ENK gene show a lower breakpoint for both normal chow and fat chow compared to WT mice [105], and they exhibit lower overall bar pressing for palatable high-fat food [173]. In contrast, they show no difference in sucrose intake or preference [96, 105, 174]. As with injection studies in outbred rodents, these data indicate that ENK may be more closely related to fat overconsumption than to sucrose overconsumption. Similarly, whereas mice lacking or overexpressing the GAL gene are similar to WT mice in their amount of chow intake [175] and sucrose preference [65, 66], they exhibit clear disturbances in their intake and preference for a fat-rich diet, with GAL knockout mice consuming less fat [66, 176] and GAL overexpressors consuming more fat [65]. Thus, GAL too appears to play a stronger role in controlling the overconsumption of fat rather than carbohydrate.

Findings with OX and MCH mutant mice suggest that these peptides are also related to palatable food intake. Mice lacking the gene for OX are less able to acquire the behavioral output necessary to procure food [177, 178], despite showing little change in the intake of laboratory chow [179]. On the other hand, one recent study has shown that OX knockout mice consume less sucrose, even when compared to WT mice with similar levels of locomotor activity [91]. This suggests that OX is more involved in the consumption of palatable foods than in food intake *per se*. Mice lacking MCH do show decreased chow intake, and consequently they weigh significantly less than WT mice [180, 181]. Although transgenic overexpression of MCH does not lead to significantly greater chow intake, it does lead to greater intake of a high-fat diet [182], confirming that this peptide, generally related to caloric intake, also has a more specific relationship with the intake of palatable food.

In contrast to ENK, GAL, OX and MCH, studies with NPY mutant mice suggest that it is related both to food intake in general, as well as to palatable food in particular. Mice lacking NPY consume less laboratory chow [93, 183] and less of a high-fat diet [184], resulting in a decreased incidence of diet-induced obesity. Further, NPY overexpressors consume more of a sucrose diet and are more likely to become obese on this diet [185]. Thus, studies using genetic knockout and overexpression generally support but also extend findings in outbred animals that use injection and gene expression techniques.

Behavioral Disturbances in Relation to Palatable Food Overconsumption

A number of behavioral tests have been shown in outbred rats to successfully predict which ones will go on to overconsume palatable diets. Using a measure of initial high-fat diet intake during a few days of access that predicts long-term intake, our laboratory has been able to classify rats at normal weight that are either high-fat consumers, which ingest 35% more calories of the high-fat than low-fat chow diet, or controls, which consume a similar number of calories of these two diets [27]. As with alcohol and nicotine, locomotor activity, particularly high locomotor activity in a novel open field, can also predict which rats will go on to consume more dietary fat [186] but not those that go on to consume more sucrose [187, 188]. On the other hand, just as with alcohol and nicotine, anxiety is a weak predictor

of future fat intake [186]. These studies suggest that early fat intake and high novelty-seeking are the best markers for predicting fat overconsumption.

Peptide Disturbances and Behavioral Predictors to Palatable Food Overconsumption

Behaviors that predict fat consumption are also linked to disturbances in peptide expression. High-fat consumers identified by early fat intake, but maintained on a chow diet, exhibit elevated expression of OX and MCH in the PFLH [186] and ENK in the PVN, NAc and central nucleus of the amygdala [27]. Although not tested, it is also very likely that these rats also have increased GAL, as fat-preferring Brattleboro rats have higher GAL mRNA in the PVN than do control Long-Evans rats [189, 190]. This same rat strain shows no difference in NPY levels in the ARC [191]. Those rats that show greater novelty-induced locomotor activity also show higher hypothalamic but not extra-hypothalamic ENK expression [79, 89], and our preliminary work suggests that they also have higher PVN GAL expression [192]. Thus, the same peptides that stimulate fat intake when centrally injected, and are themselves increased by fat intake, may already be more active in animals likely to go on to overconsume dietary fat when chronically available.

Physiological Disturbances in Relation to Palatable Food Overconsumption

High levels of the circulating lipids, TG, can also predict which subjects will overconsume a high-fat diet [107]. As described above, rats with high TG after the same small, high-fat meal have been found to have elevated OX and MCH expression in the PFLH and both ENK and GAL in the PVN, with no difference in NPY in the ARC [79, 107]. Peptide levels for OX and MCH are also increased [107]. Therefore, even when animals have consumed an identical meal, those that have higher levels of circulating lipids after the meal and are predicted to overconsume fat are found to exhibit greater expression and levels of the same peptides that specifically stimulate fat intake.

VI. CONCLUSION

The reviewed literature points to several commonalities among the neurochemical, behavioral and physiological disturbances associated with and possibly casually related to the overconsumption of ethanol, nicotine and palatable food. With the exception of NPY which shows a strong inverse relationship with ethanol and nicotine consumption, the orexigenic peptides GAL, ENK, OX and MCH in the PVN and PFLH each play a specific role in promoting the consumption of these substances and, in turn, are further stimulated by their ingestion, This positive relationship seems to occur predominantly and consistently in hypothalamic regions, such as the PVN and PFLH, rather than in mesolimbic structures or the ARC in the basal hypothalamus, suggesting that the increased activity of the specific orexigenic peptides in dorsal hypothalamic areas may have particular importance in driving the common tendency to overconsume both the drugs and palatable foods. Building on this positive feedback circuit, the literature further demonstrates that the specific peptides in the PVN and PFLH may be disturbed in overconsuming animals even *prior to* any exposure to drugs or palatable food. Moreover, these hypothalamic peptides, with ENK and OX showing the most consistent results, tend to be positively related to increased locomotor activity, novelty-seeking, early consumption patterns, and circulating lipids, all factors that are

effective in predicting an animal's propensity to consume excess amounts of these drugs or food. Based on the outlined literature, we conclude that drugs of abuse, including ethanol and nicotine which have limited or no caloric value, and also palatable foods, particularly those rich in fat or sugar, are overconsumed by animals with similar inherent disturbances in positive feedback circuits of the hypothalamus.

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Future Research Questions

- Since the consumption of nicotine may share similar peptide circuits with ethanol and fat, with each stimulating the intake of the other, future research should examine the influence of nicotine on the consumption of ethanol and fat, and vice versa.
- Evidence shows that animals exhibiting increased locomotor activity, novelty-seeking, early consumption patterns, and circulating levels of lipids, may go on to consume greater amounts of drugs or palatable foods. Future studies should be aimed at examining how manipulating these behavioral traits themselves may lead to changes in consummatory behavior. Since certain peptides appear to be altered in animals showing these traits, studies should further explore how altering the activity of these peptides may affect not only the behaviors but also the ingestion of drugs and palatable foods.
- With research showing that hypothalamic peptides within the PFLH and PVN are important in driving consummatory behavior, possibly prior to any substance exposure, one important future step would be to measure the status of these peptides in several well-established animal models known to consume increased amounts of ethanol, fat or even nicotine.

Key Learning Objectives

- Similar peptides within the PVN and PFLH stimulate the consumption of ethanol, palatable foods and sometimes also nicotine, and the peptides themselves are also stimulated by the consumption of these substances.
- Behaviors related to locomotion, novelty-seeking and early consumption patterns are influenced by peptides within the PVN and PFLH and can drive future consumption of certain drugs and palatable foods.
- Circulating TG levels are consistently elevated in animals predicted to consume increased amounts of ethanol, fat and possibly nicotine.
- Inherent disturbances in hypothalamic feedback circuits may predispose animals to drug and palatable food overconsumption.