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Overconsumption of dietary fat and alcohol: Mechanisms involving lipids and hypothalamic peptides

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Abstract

The studies described in this report provide interesting animal models for exploring some of the metabolic and neural antecedents to the over-consumption of fat and alcohol. The results provide strong support for the existence of positive feedback loops that involve a close relation between circulating lipids and orexigenic peptides in dorsal regions of the hypothalamus. The peptides involved in these circuits include galanin, enkephalin, dynorphin and orexin. These peptides are expressed in the paraventricular nucleus and perifornical lateral hypothalamus, and they have very different functions from peptides expressed in the arcuate nucleus. Through mechanisms involving circulating lipids that rise on energy-dense diets, these peptides in the dorsal hypothalamus are each increased by the consumption of fat and ethanol; these nutrients, in turn, stimulate further production of these same peptides that promote overeating and excess drinking. These mechanisms involving non-homeostatic, positive feedback circuits may be required under conditions when food supplies are scarce and periods of gorging are essential to survival. However, they have pathological and sometimes life-threatening consequences in modern society, where fat-rich foods and alcoholic drinks are abundantly available and are contributing to the marked rise over the past 25 years in obesity and diabetes in both children and adults.

1. Introduction

There are a variety of peptides in the brain that have been found to have significant stimulatory effects on ingestive behavior [1]. This review addresses a specific question, whether these peptides within the hypothalamus have a role in mediating the over-consumption of fat and alcohol that may contribute to the development of obesity and alcoholism. The specific peptides described in this review, which are positively linked to fat and alcohol, are galanin (GAL), the opioid peptides enkephalin (ENK) and dynorphin (DYN), and the orexins (ORX). These different peptides which stimulate ingestive behavior are expressed in a number of neuronal populations throughout the hypothalamus, including the paraventricular nucleus (PVN), perifornical lateral hypothalamus (PFLH), and arcuate nucleus (ARC). These orexigenic peptides differ from others, such as neuropeptide Y (NPY), which are expressed almost exclusively in neurons of the ARC and have a weak or inverse relation to fat and alcohol. This review first describes the GAL system as it relates to ingestive behavior and differs from NPY in this relationship. It then summarizes some recent findings showing the opioid peptides, ENK and DYN, and ORX to be similar to GAL in their relation to ingestive behavior. The evidence described herein supports the existence of non-homeostatic, positive feedback circuits, which

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link these hypothalamic peptides to both fat and alcohol and likely contribute to their over-consumption. In addition to a stimulatory effect of these peptides on the ingestion of nutrients, these feedback circuits involve a stimulatory effect of the ingested fat and alcohol on the expression and production of these peptides in the hypothalamus. It is proposed that these vicious cycles play an important role in mediating the excess consummatory behavior that occurs under conditions where fat-rich foods and alcoholic drinks are abundantly available.

2. Effects of galanin on ingestive behavior

Injection studies reveal a number of effects of GAL on behavioral responses, in addition to endocrine and metabolic systems [1-7]. The first behavioral investigation with acute GAL injection revealed a stimulatory effect of this peptide on food intake in rats [4]. This effect is strongest when GAL is administered directly into the PVN, and the opposite effect, a suppression of food intake, is seen with injection of compounds that block GAL receptors or GAL synthesis. While robust and confirmed in multiple studies, this GAL response is found to be smaller and of shorter duration than that seen with injection of NPY, another peptide found two years earlier to stimulate feeding in rats [1,8]. This provided the first evidence that these two orexigenic peptides in the hypothalamus may have different functions in their effects on energy balance.

In addition to the magnitude of their feeding responses, GAL differs from NPY in the specific nature of its feeding response. Whereas GAL injection has little effect on an animal's preference for the macronutrients, carbohydrate, fat, or protein, a variety of evidence links this peptide's feeding-stimulatory response specifically to dietary fat [7,9-14]. In contrast to NPY which has been linked to carbohydrate intake, the GAL-elicited feeding response is closely related to dietary fat. It is stronger and more prolonged in subjects maintained on a high-fat compared with a low-fat diet and in subgroups or strains of rats that naturally prefer fat. It is greatly attenuated when fat is removed from the diet. Also, the GAL-induced feeding effect on a fat-rich diet is suppressed by injection of the pentapeptide enterostatin, which increases c-Fos immunoreactivity in the PVN, and by the GAL antagonist M40, both of which reduce the consumption of fat. Moreover, PVN injections of antisense oligonucleotides to GAL mRNA, which decrease GAL peptide levels, produce a marked reduction in fat ingestion. This is consistent with the idea that GAL-induced feeding has a specific relation to dietary fat and thus may contribute to the large meal size and overeating generally associated with fat-rich foods.

In addition to stimulating food intake, there is evidence that central injection of GAL also increases the consumption of ethanol [15,16]. This effect, which contrasts with the suppressive effect generally seen with NPY [17], occurs with GAL injection into the ventricles as well as directly into the PVN and both in the presence and absence of food and water. Also, the opposite effect, a marked decrease in alcohol intake, can be observed with injection of the GAL antagonist, M40. These results suggest that peptides in the hypothalamus that modulate food intake may also have a role in controlling the consumption of ethanol. Clinical evidence for the involvement of endogenous GAL in alcohol intake is supported by a report demonstrating an association of GAL haplotypes with alcoholism in distinct populations [18].

To date, studies with GAL mutants indicate that mice with deletions of the GAL gene or GAL receptor genes or that overexpress GAL are able to defend their food intake and body weight when fed *ad libitum* on a low-fat diet or even fasted on this diet [19,20]. Whereas this suggests that GAL may not have a major role under these conditions, this lack of response in GAL mutants, as with animals receiving chronic GAL injections, may be attributed to other factors. These may be the activation of compensatory mechanisms that help to maintain nutrient homeostasis or the lack of sufficient fat in the diet, an important variable for revealing GAL's physiological and behavioral actions (see above). Since GAL is believed to function

specifically under conditions when dietary fat is in excess, GAL mutants may exhibit disturbances in feeding and body fat accrual only when maintained on a high-fat diet or pure macronutrient diets that allow animals to express their natural preferences for fat as compared with carbohydrate or protein. Studies to date have only examined the GAL mutants on standard lab chow diets that are low in fat. A specific effect that was observed in these GAL knockouts was an increased sensitivity to the inhibitory effects of chronic leptin treatment on body weight and fat mass [21]. This result suggests that endogenous GAL may have a role in promoting weight gain. This effect has recently been described in rats receiving chronic PVN injections of GAL, and in support of the close relationship between GAL and dietary fat, it occurs specifically on a high-fat diet but not a low-fat diet [14].

3. Effects of diet, alcohol and nutrients on hypothalamic galanin

Further evidence indicates that endogenous GAL is highly responsive to manipulations of diet and nutrients as well as hormones but responds very differently from NPY, further reflecting functional differences between these peptides [1,6-8,22-25]. In contrast to NPY which is highly responsive to conditions of negative energy balance and low-energy diets, GAL is stimulated under conditions of positive energy balance related specifically to dietary fat. This is seen, for example, in their different responses to various hormones. The adrenal steroid corticosterone, which rises when energy stores are low, has little impact on or transiently inhibits GAL gene expression in PVN neurons as well as GAL-induced feeding response; this is in contrast to its effects on NPY, which include a marked stimulation of the endogenous peptide in the ARC and the feeding response induced by PVN NPY injection. The gonadal steroid estrogen, either alone or in combination with progesterone, also has different effects, potently and consistently stimulating GAL but having weak or inverse effects on NPY. These two peptides also differ in their responses to the adipose tissue hormone, leptin. This hormone has a strong inhibitory effect on NPY in the ARC but produces only a small suppression of GAL mRNA in the PVN and has little or no impact on GAL expression in the ARC, GAL release from hypothalamic explants, and GAL-induced release of corticotrophin-releasing factor. This differential responsiveness of these peptides to leptin administration may help to explain their different responses that occur under physiological conditions involving a spontaneous rise or fall in leptin. That is, a deprivation-induced decrease in leptin has little impact on or suppresses GAL mRNA, while it markedly enhances NPY expression. Also, a rise in leptin in obese animals consistently suppresses NPY while stimulating GAL mRNA in the PVN. These clear differences between these orexigenic peptide systems suggest that they may function in different physiological states or conditions and through distinct mechanisms.

Marked differences between GAL and NPY are also evident in studies examining the effects on endogenous peptides of the dietary nutrients and anti-metabolites that affect their metabolism. One main finding in a number of studies and animal models is that endogenous GAL gene expression and peptide production in the PVN, similar to the feeding response induced by exogenous GAL, are closely related to dietary fat [1,5,6,9,13,25]. They are positively correlated with the amount of fat consumed and are stimulated by acute or chronic consumption of a mixed high-fat diet, either liquid or solid. Also, they are elevated to peak levels during the middle of the feeding cycle and around puberty when preference for fat naturally rises. This is in contrast to NPY in the ARC, which is unaffected or reduced by fat consumption, is positively correlated with carbohydrate intake, and peaks two hours prior to onset of the nocturnal feeding cycle when carbohydrate is the preferred macronutrient [1].

A major consequence of fat consumption is a rise in levels of circulating lipids, particularly triglycerides (TG) [7,25-28]. This metabolite increases in direct proportion to the amount of fat consumed. This effect is evident under chronic feeding conditions, with hypertriglyceridemia a common trait in animals and humans that overeat a fat-rich diet. It is

also seen in acute feeding paradigms, with TG levels rising higher and remaining elevated for longer periods after fat-rich meals. In recent studies, GAL in the PVN but not NPY is found to be strongly, positively related to circulating levels of TG, in addition to their uptake and metabolism in muscle [1,5-7,25]. This relationship is robust, seen in different models of dietary obesity and even under conditions of acute exposure to a high-fat diet, for one day or even one hour, indicating its independence of changes in body weight and leptin. Injection of the fat emulsion, Intralipid, which increases TG levels, stimulates GAL expression and c-Fos immunoreactivity in the PVN but has no effect on NPY expression or c-Fos in the ARC [25, 29]. Further, fat-preferring obesity-prone rats and mice compared with carbohydrate-preferring animals exhibit higher levels of circulating TG and elevated GAL in the PVN, while NPY is unaffected or reduced [6,7,30,31]. They are also more responsive to the feeding-stimulatory effects produced by GAL but not NPY injection [6,12,14,32]. A direct relationship between GAL and the metabolism of fat is suggested by evidence that pharmacological blockade of fat oxidation, while having no impact on NPY, reduces PVN GAL expression while suppressing fat intake, and it stimulates the expression of GALR1 in the PVN [1,33]. Conversely, GAL shows little change after pharmacological blockade of glucose oxidation, which has a potent stimulatory effect on NPY. This evidence suggests that endogenous GAL functions specifically under dietary conditions rich in fat and in response to signals related to circulating TG and fat metabolism. This positive relation of PVN GAL to dietary fat, together with the finding that PVN GAL injection produces a stronger feeding response on fat-rich diets, suggests that this peptide may function within a non-homeostatic positive feedback loop or vicious cycle. In this loop, GAL stimulates intake of a fat-rich diet which increases the production of endogenous GAL that, in turn, promotes further eating.

There is evidence that this bidirectional relationship between GAL and fat may be similarly seen for GAL in relation to ethanol. In addition to the stimulatory effect of GAL injection on the consumption of ethanol (see above), recent studies demonstrate that GAL expression in the PVN, but not NPY in the ARC, is stimulated in rats injected with 10% ethanol or induced to drink ethanol [34]. Further, levels of PVN GAL mRNA are positively correlated with the amount of ethanol consumed and blood alcohol levels, and naloxone-induced withdrawal from the opioid effects of ethanol ingestion reverses this ethanol effect on GAL, significantly reducing peptide expression below baseline levels. These studies with measures of endogenous GAL, together with those involving GAL injection, support the existence of a positive relationship between this peptide and alcohol, one that may contribute to the over-consumption of ethanol. This GAL-alcohol feedback loop, which may involve elevated TG levels induced by ethanol intake [35], operates in a non-homeostatic manner similar to that suggested for the GAL-fat feedback loop. In this loop, GAL stimulates the drinking of ethanol which in turn stimulates the expression of this peptide that induces further drinking.

4. Neural site of galanin's action

As indicated above, the feeding response induced by GAL injection is strongest when this peptide is administered directly into the PVN [1,4,6,36]. This feeding effect is most robust in the medial parvocellular division of this nucleus, and it sharply diminishes in magnitude as the injection site moves to the lateral PVN and then beyond this nucleus in all directions. The studies of endogenous GAL show that the stimulatory effect of dietary fat, lipid injection, or ethanol intake on GAL expression also occurs in the medial parvocellular division of the PVN, most particularly its anterior region [5,7,9,29,32,34]. It is not detected in the caudolateral PVN, where the magnocellular neurons are concentrated, nor is it seen in the ARC. These findings suggest that the PVN may be a primary site involved in promoting ingestive behavior linked to the GAL-mediated, positive feedback circuit. The importance of this PVN GAL system in non-homeostatic consummatory behavior is supported by evidence that GAL-induced feeding is attenuated by PVN lesions or GAL antagonists and that the consumption of a fat-rich diet

or alcohol is reduced by local injections of compounds that block GAL synthesis, release, or receptor function [5,6,9,15,16]. This indicates that this nucleus contains the peptide neurons that respond to dietary fat or alcohol, in addition to the peptide receptors that promote the overeating of palatable, fat-rich foods or drinking of alcohol. Thus, GAL may function, in part, through local circuits involving cells and fibers in the PVN that act as interneurons to regulate its own expression and release [37].

5. Relation of opioid peptides to dietary fat

Further investigations suggest the existence of other neural substrates, involving opioid peptides in the hypothalamus, which are associated with dietary fat and possibly involved in the overeating of a fat-rich diet. Central injections of the opioids ENK and DYN, similar to GAL, stimulate feeding in a dose-dependent manner, and this effect is particularly strong in the PVN, although it also occurs in the forebrain [1,5,36,38,39]. These opioid peptides stimulate intake of a high-fat diet more than a low-fat diet, and in some studies, they preferentially increase the ingestion of pure fat more than carbohydrate, independently of baseline preference [36,40]. A role for endogenous opioid systems in the feeding process is supported by evidence that feeding of a fat-rich diet and a preferential increase in fat intake are reduced by both peripheral injection of opiate antagonists and central injection of selective antagonists of mu and kappa but not delta opioid receptors [40-43]. The finding that GAL-induced feeding is blocked by an antagonist of opioid receptors [8,44] supports the idea that PVN GAL in producing overeating acts through a local opioid circuit, even possibly within the same neurons that synthesize the opioid peptides.

Recent studies of the endogenous opioid peptides in the hypothalamus reveal a similar effect of dietary fat on these peptides as that described for GAL [29,45-48]. The ingestion of a high-fat diet increases gene expression of both ENK and DYN in the hypothalamus, and the strongest and most consistent effect is seen specifically in the PVN. In this nucleus, ENK and DYN are increased by 50-100% after 1 week, 1 day, 60 min and even 15 min of high-fat diet consumption. In the ARC, these peptides are considerably less responsive, exhibiting no change in response to the briefer periods of diet intake [29,45,48,49]. The stimulation by dietary fat of opioid gene expression in the PVN is accompanied by an increase in opioid peptide levels as measured by radioimmunoassay. This suggests that the increased mRNA levels enhance the production and possibly the release of these peptides, allowing them to have functional consequences in the PVN.

This stimulatory effect of dietary fat on PVN opioids can be observed without a change in daily caloric intake, body weight or body fat and also in levels of the hormones, insulin or leptin, which rise with body weight [29]. This focuses attention on a possible role for the opioids in acute, perhaps non-homeostatic processes involved in enhancing food intake. Further tests show that the opioids are stimulated by a single fat-rich meal that is equal in caloric density and palatability to a low-fat control meal [45]. This indicates that the effect of dietary fat on endogenous opioids does not reflect the greater palatability or energy density which is characteristic of this diet [50,51]. This is further supported by evidence showing a similar change in endogenous opioids with peripheral injection of the lipid emulsion, Intralipid, which bypasses the ingestion process and avoids stimuli related to palatability [29,45].

Additional findings suggest that post-ingestive factors, such as circulating lipids, may be important in determining the expression level and functions of the opioids in the PVN, similar to GAL. This is demonstrated by results revealing a strong and consistent association between the opioids and a marked rise in circulating TG levels induced by fat consumption as well as injection of Intralipid [29,45]. Although the molecular mechanisms elevating ENK and DYN transcripts in response to fat remain to be characterized, evidence demonstrates a direct

stimulatory effect of short-chain fatty acids on ENK gene expression in PC12 rat cells via an intact PKA signaling pathway, with a possible involvement of lipid-activated transcription factors [52]. Fatty acids may also modulate the binding of opioid peptides to their receptor [53]. This evidence indicates that opioids in the PVN, as shown for GAL, are responsive to circulating lipids, TG or fatty acids, which may mediate the stimulatory effect of dietary fat on these peptides. Together with the results showing PVN opioid injections to have a potent stimulatory effect on fat consumption, these findings support the existence of a positive feedback loop and a role for this circuit in the overeating induced by dietary fat.

These findings suggest that the opioids and GAL in the hypothalamus function in a similar manner and possibly interact in the process of stimulating feeding behavior [1,5]. These peptides act within the same brain site, namely the PVN, and there is evidence that GAL is co-localized with DYN in neurons of this hypothalamic nucleus [54]. Also, feeding induced by GAL is blocked by injection of an opioid antagonist [8,10,55]. Thus, GAL may promote overeating on a high-fat diet, in part, through stimulation of the endogenous opioid peptide systems that, in turn, may act through other downstream systems, such as dopamine, as described below.

6. Relation of opioid peptides to alcohol intake

The similarities between GAL and opioids in relation to dietary fat suggest that these peptides may also be similar in their relation to ethanol intake [5]. In terms of the effects of the opioids, the drinking of ethanol is found to be stimulated by peripheral injection of the opioids, morphine or leu-ENK, and it is reduced by administration of opioid receptor antagonists [5,56-58] or deletion of the kappa-opioid receptor gene [59]. In reverse, a positive relationship is detected between ethanol consumption and the endogenous opioids in the hypothalamus. While earlier studies of endogenous opioids in whole hypothalamus yielded mixed results, ENK mRNA in the PVN was shown to be significantly stimulated after 24 hours by acute intragastric infusion of 30% ethanol [60], while unaffected by intake of 5% ethanol [61]. In a recent report [62], a strong, stimulatory effect of ethanol on PVN opioids has been described. Rats voluntarily drinking 9% ethanol (1.0-2.5 g/kg/day) show a significant increase in expression of both ENK and DYN in the PVN, similar to that seen with GAL. They also exhibit an increase in opioid peptide levels in the PVN as measured by radioimmunoassay. This indicates that the ethanol-induced change in gene expression results in a corresponding increase in peptide production that may have behavioral effects. A similar change in gene expression is observed with acute injection of 10% ethanol (1.0 g/kg), supporting a direct effect of this nutrient. The possibility that these elevated peptides have functional consequences needs to be confirmed with opioid injection studies in the PVN, similar to those performed with GAL [15,16].

There is evidence that ethanol like dietary fat can increase circulating levels of TG [35,62, 63]. The injection as well as consumption of ethanol in rats consistently increases circulating levels of TG, together with blood levels of alcohol [62]. This elevation in TG may be attributed, in part, to the fact that ethanol reduces the clearance of very low-density lipoproteins-TG and chylomicrons-TG from the blood [64,65] and decreases fat oxidation in the body [65]. This is supported by the finding that TG and alcohol levels in blood of ethanol-drinking rats are strongly, positively correlated with each other, as well as with the amount of ethanol consumed [62]. They are also closely related to opioid as well as GAL peptide expression in the PVN, supporting the involvement of these nutrients in the ethanol-induced increase in endogenous peptides. Together with the evidence that injections of opiate agonists increase ethanol intake, these findings once again suggest the existence of a positive feedback loop involving circulating lipids and alcohol that stimulate endogenous opioids and promote further consumption of ethanol. While the hypothalamic PVN appears to have a prominent role in this process, it is of interest that that acute and chronic ethanol consumption can also stimulate the

expression of DYN in the forebrain, specifically the nucleus accumbens (NAc) [66]. This contrasts, however, with evidence that ENK and GAL expression in this structure, both shell and core, along with the dorsal striatum are unaffected or actually reduced by chronic ethanol consumption [61,62,67,68]. These results reveal clear differences between the peptidergic systems of the hypothalamus and the forebrain.

These circulating nutrients, alcohol and TG, may function together through a common mechanism, specifically in the PVN, that underlies their similar effects on the peptides. This is supported by evidence that the peptide effect induced by ethanol or dietary fat is anatomically specific, seen in the PVN but generally weak in the ARC [7,25,29,34,62]. It is possible that ethanol and TG act indirectly on PVN neurons through some common effect on peripheral fat metabolism. This does not appear to be the case, as fat oxidation is stimulated by dietary fat [7] while suppressed by ethanol [65]. Since ethanol and fatty acids can have direct effects on central neural processes, including enzyme activity, neural activity and gene expression [44, 69-71], studies with central administration of these nutrients should help to elucidate their specific roles in the peptide-induced changes observed here. There is evidence showing the adipocyte hormone, leptin, to be associated with craving for alcohol and lifetime alcohol intake [72] and fasting insulin levels to be inversely related to ethanol intake [73]. However, rats voluntarily drinking 9% ethanol or receiving acute injections of 10% ethanol show little change in levels of these hormones and little relation of these hormones to the hypothalamic peptides [62]. This finding suggests that leptin and insulin have little role in the ethanol-induced increase in PVN opioid peptides, underscoring the specificity of the change in TG and their impact on the brain.

7. Relation of orexins to dietary fat and alcohol intake

The ORX peptides are multifunctional. They have been implicated in diverse aspects of behavior, such as food intake, reward, sleep and recently alcohol intake. Specifically, recent studies demonstrate that ORX, which is expressed primarily in the PFLH, is very similar to GAL and the opioids in their relation to dietary fat and alcohol [1,25,74-79]. The injection of ORX-A into the hypothalamus stimulates feeding, and this response is significantly stronger on a high-fat compared to low-fat diet [76]. Further, endogenous expression of ORX in the PFLH, in close association with a rise in TG levels, is stimulated by ingestion of a high-fat diet, by injection of a fat emulsion, and in rodents that are prone to obesity [25,77-79]. In studies with ethanol-preferring rats, peripheral injection of an orexin receptor antagonist is found to abolish cue-induced reinstatement of ethanol-seeking behavior, while chronic consumption of ethanol increases the area of expression of ORX in the PFLH [74]. Consistent with these studies are unpublished results from this lab (S.F. Leibowitz and G.-Q. Chang) working in collaboration with a laboratory at Princeton University (B.G. Hoebel and E. Schneider). In Sprague-Dawley rats trained to voluntarily drink unsweetened 10% ethanol, the injection of ORX-A vs saline vehicle directly into the PVN or PFLH is found to significantly increase the consumption of ethanol. Also, ORX gene expression in the PFLH is stimulated in ethanol-drinking compared to water-drinking rats. Thus, similar to GAL and the opioids in the PVN, ORX in the PFLH functions within positive feedback loops that may control the consumption of ethanol and fat-rich diets. Whereas GAL is similarly stimulated in the PFLH as well as PVN by dietary fat, double-labeling immunofluorescence studies [77] show that ORX and GAL neurons are anatomically distinct and thus are likely to function independently in these systems.

8. Hypothalamic peptides in relation to dopamine

There is further evidence suggesting a role for mesolimbic dopamine (DA) in the over-consumption of a high-fat diet or alcohol induced by PVN peptides. Whereas DA itself has only a weak-to-moderate effect in initiating feeding, this catecholamine is believed to have a

primary function in the motivation to eat palatable foods, specifically producing arousal and enhancing an already established feeding response [80,81]. Its involvement in fat-induced hyperphagia and alcohol consumption is supported by evidence that DA in the NAc is released by consumption of a palatable, fat-rich diet and ethanol [82,83]. Also, DA is stimulated by injection of the orexigenic peptides, GAL, opioids and ORX [84-89]. These hypothalamic peptides in the PVN and PFLH may act through projections coursing rostrally to DA terminal sites in the forebrain or, more likely, caudally to DA neurons in the ventral tegmental area (VTA) [90]. These DA neurons project to the NAc and release DA in the shell of this nucleus, where it functions in relation to the novelty of a reward, and in the core, where it relates to the directional/discriminative aspects of instrumental responding [80]. A role for this hypothalamicVTA-NAc neurocircuit in controlling food intake is supported by the findings that the GALR1 receptors possibly involved in the feeding response are densely concentrated near DA neurons in the VTA [91], VTA injection of a general opioid antagonist blocks feeding induced by PVN injection of an opioid agonist [92], and ORX-containing projections to DA neurons in the VTA are directly involved in the rewarding effect of opioid stimulation [93]. Thus, DA signaling in the NAc, an important modulator of motivated behavior, is likely to have a role in mediating the stimulatory effects of the hypothalamic peptides on the consumption of palatable, fat-rich diets and ethanol.

9. Pathophysiological consequences of dietary fat, TG and orexigenic peptides

With dietary fat and ethanol increasing the production as well as gene expression of the orexigenic peptides, one is led to consider the functional consequences of these elevated peptides as they operate within the positive feedback loops proposed above. There is extensive evidence in animals and humans showing that dietary fat produces hyperphagia, generally a 10-15% increase in caloric intake [7,25,28,94]. This fat-induced hyperphagia is evident in chronic feeding paradigms, with total daily intake and meal size rising in direct proportion to the amount of fat in the diet. It is also seen in acute feeding paradigms, with a small high-fat meal (10-15 Kcals) compared to an equal calorie low-fat meal being followed by a shorter post-meal interval and increased food intake in subsequent meals [25,95-98]. This acute hyperphagia occurs whether the fat-rich meal is presented in solid or liquid form, infused intragastrically, injected as a fat emulsion, or given in a sham-feeding paradigm. Fat has long been known to be less satiating than protein and carbohydrate, possibly due to the fact that fat intake is less tightly regulated, with lipids less readily oxidized and more easily stored in large fat depots [50]. Fat is also more palatable than carbohydrate and protein, perhaps due to its caloric density and texture, and it enhances their palatability when mixed with these macronutrients. These sensory properties may not be critical factors, however, as hyperphagia induced after a high-fat meal compared to a low-fat meal can occur even when these diets are similar in palatability and energy density.

Circulating lipids such as TG and fatty acids, which invariably rise with acute and chronic intake of fat, are known to interfere with physiological and neural processes and thus may be involved in the fat-induced increase in consummatory behavior. These lipids are elevated with different psychological disorders, such as stress-related overeating and certain eating disorders [99-101], and they contribute to complex metabolic disturbances along with cardiovascular disease and low-grade systemic inflammation [102]. They disturb the release, actions, and transport into brain of certain hormones, e.g., leptin, which normally reduce food intake [103] and inhibit hypothalamic peptides that stimulate feeding (see above). Direct support for the idea that elevated TG levels contribute to the overeating on fat-rich diets is provided by evidence that food intake as well as TG is significantly greater after injection of the fat emulsion, Intralipid, compared with an equicaloric glucose solution [25,98].

With the fat-stimulated peptides invariably elevated by acute or chronic consumption of a high-fat diet and higher TG levels, they are likely to be important and active participants in the increased caloric intake induced by fat-rich diets. This has been most clearly demonstrated in studies of GAL in the PVN. Along with circulating TG, this peptide is increased in rats that show a preference for fat when given pure macronutrient diets or that overeat calories on a mixed, fat-rich diet [5-7]. A pathophysiological consequence of the overeating of fat is generally an increase in weight gain and accrual of body fat [7,28]. This can occur even in rats receiving a single, daily fat-rich meal, compared to those given a low-fat meal that is equal in calories, energy density and palatability [25]. There is recent evidence that chronic GAL injections in the cerebroventricles or PVN increase body weight and body fat along with daily food consumption and TG levels [14,21]. Conversely, repeated PVN injections of antisense oligonucleotides to GAL mRNA markedly reduce fat intake and weight gain, in conjunction with a decline in PVN GAL levels [6,9]. The importance of fat in revealing these effects of GAL is evident in the findings that GAL injection stimulates feeding and body weight on a high-fat diet (45-60% fat) but not a low-fat diet (10% fat) and that endogenous GAL is elevated in rats that become obese and have elevated TG on a high-fat diet but not in rats that develop obesity with normal TG levels on a low-fat diet [1,7,14,31]. This leads one to question the specific function of GAL in states of positive energy balance on a fat-rich diet. There is evidence that GAL on this diet acts both physiologically and behaviorally, to counteract the metabolic disturbances caused by excess fat and also to compensate for the deficiency of carbohydrate in the diet. In addition to reducing energy expenditure, this peptide enhances the capacity of muscle to utilize the small amount of available carbohydrate, and it increases food intake in general to provide more of the essential carbohydrate [1,14]. In addition to these effects, GAL together with the opioids and ORX are likely to contribute to the rewarding value of foods and fluids through mechanisms involving the release of DA in the forebrain (see above).

10. Positive relation of dietary fat to ethanol intake

As described above, circulating TG and hypothalamic peptides rise with the consumption of ethanol as well as fat, supporting a role for the positive feedback loops between diet and peptide in promoting the over-consumption of ethanol as well as fat-rich diets. Similarities in the nature of their operation and sites of action within the hypothalamus further indicate that these mechanisms for ethanol and fat intake may functionally overlap and possibly interact in this process. In addition to ethanol consumption stimulating caloric intake [104], there is accumulating evidence suggesting a close, positive relationship between the eating of fat and drinking of ethanol. In animal studies, rats maintained on a high-fat diet or exhibiting a preference for fat are found to consume more ethanol [105-107]. Further, clinical studies show that fat intake is elevated in ethanol drinkers, with bingeing on fat-rich foods associated with high rates of alcoholism [104,108]. Also, drinkers maintained on a fat-rich diet compared to a carbohydrate-rich diet exhibit shorter periods of abstinence from ethanol [109,110].

A direct and possibly causal relationship between dietary fat and ethanol intake is demonstrated by a recent report in rats [105]. This study demonstrates that a high-fat meal compared with a low-fat/high-carbohydrate meal can significantly increase ethanol intake right after the meal. Moreover, injection of Intralipid compared with glucose or saline produces a similar avidity for ethanol, revealing the effect of fat in the absence of taste. While the palatability of a high-fat meal may potentiate ethanol intake by activating orosensory-reward systems, perhaps involving the opioids [111-113], the findings with Intralipid injection, which bypasses the orosensory system, indicates that the fat-induced increase in ethanol consumption can not be attributed solely to taste. It very likely involves postingestive factors, presumably related to circulating lipids or fat metabolism, which potentiate the hypothalamic peptides.

11. Conclusions

This developing body of science, relating circulating nutrients to hypothalamic peptides, holds great promise for providing a more fundamental understanding of the multiple feedback systems that underlie pathological patterns of eating and drinking and consequent disturbances in weight gain, in children as well as adults. This research should facilitate the design of more precise approaches for studying and addressing the growing incidence of eating and body weight disorders within modern societies where fat-rich foods as well as alcoholic drinks are abundantly available.

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