Sugars and Fats: The Neurobiology of Preference

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ABSTRACT The appetite for specific foods and nutrients may be under neuroregulatory control. In animal studies, fat intake is increased by both opioids and galanin and reduced by enterostatin, whereas carbohydrate intake is increased by neuropeptide Y (NPY). However, what may be affected is the consumption of preferred foods rather than macronutrients. Fat and sugars are highly preferred whether consumed separately or as mixtures in foods. Studies suggest that sustained consumption of sugars and fats may have additional metabolic consequences; among these are neurochemical changes in brain sites involved in feeding and reward, some of which are also affected by drugs of abuse. Furthermore, the consumption of fats and sugars alters tissue expression of uncoupling proteins, which are also influenced by neuroregulatory peptides and may be markers of energy expenditure. These data suggest that these palatable nutrients may influence energy expenditure through changes in central neuropeptide activity. Fats and sugars could affect central reward systems, thereby increasing food intake, and might have an additional effect on energy expenditure. Such palatable substances may contribute to the observed increase in the body weight of populations from affluent societies during the past few decades. J. Nutr. 133: 831S–834S, 2003.

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The concept of “one peptide—one macronutrient” has posited that a given neuropeptide controls dietary preferences for a specific macronutrient. In animal studies, morphine and other opioid agonists increased the consumption of fat more potently than the consumption of carbohydrate when the two were offered concurrently, in the form of complete diets or as individual macronutrients (1–4). Neuropeptide Y (NPY)3 increased carbohydrate intake more strongly when offered together with fat (5). Enterostatin only decreased food intakes of animals chronically maintained on a high fat diet (6).

Appetite for sugar and fat

The concept of macronutrient preference is not concordant with human studies. Humans rarely request pure sugars or pure fat; instead they select foods such as candy or ice cream. Although hard candy, soft drinks, bread and pasta contain sugars and starch, humans react to the taste and texture of foods rather than their chemical content. Texture, temperature, color and appearance all play a role in food acceptance. Tordoff (7) recently found that the availability of foods might negate physiological controls of ingestion. Rats ingested more sucrose when given five bottles of sucrose and one bottle of water than when given five bottles of water and one bottle of sucrose (even though rats do not drink more than a bottle of fluid per day).

An animal’s food preferences may thus modify the impact of a neuroregulatory agent. Morphine increased intake of a preferred diet rather than selectively increasing intake of a high fat diet (8). Rats that were offered a high fat diet and a high carbohydrate diet were classified into carbohydrate-, fat- or intermediate preferers based on daily food intakes. They were then injected with morphine or saline and offered both diets. Morphine induced intake of fat in rats that preferred fat at baseline; induced intake of carbohydrate in rats that preferred carbohydrate at baseline and had no effect in rats that demonstrated no preference.

Animals exhibit a wide range of food preferences. Some rats prefer lard to corn oil when mixed into a diet. To determine whether morphine-stimulated (1, 3 and 10 mg/kg) food consumption could be modulated by dietary fat source, Glass et al. (9) provided rats with a choice between a high fat and high carbohydrate diet, using three sources of dietary fat: vegetable shortening, lard and corn oil. Under normal feeding conditions, rats selected the high fat as opposed to the high carbohydrate diet when the fat was provided by vegetable shortening.
ing or lard. Fat and carbohydrate intakes did not differ when
the fat was supplied by corn oil. Morphine increased the
percentage of dietary fat relative to baseline intakes only for
the more preferred diets containing vegetable shortening or
lard. Morphine did not stimulate fat consumption in the
less-preferred corn oil condition, suggesting that morphine
increases the consumption of total energy or preferred diets but
not the consumption of fats per se.

Other rats may prefer sugars to cornstarch. In another study
(13), food consumption was stimulated by deprivation or by
the administration of NPY. Rats were provided with a high fat
diet and with a high carbohydrate diet containing sucrose,
polyose or cornstarch. Spontaneously feeding rats ate more of
the high carbohydrate diet when sucrose or polyose was the
carbohydrate source. The high fat diet was preferred when the
main source of carbohydrate was cornstarch. Food-deprived
rats followed a similar pattern of preferences and food con-
sumption. NPY-injected rats ate more of both the high fat and
high carbohydrate diets containing sucrose and the high fat
diets were offered concurrently. In that case, the consumption
of the high fat diet did not increase. Although NPY administra-
tion and carbohydrate source each influenced diet selection, carbohydrate source had a more marked effect.

Blockade of the opioid receptor was first noted to decrease
fat consumption more effectively than carbohydrate consump-
tion (11,12). However, naloxone was much more effective in
decreasing intake of a high sucrose diet than a high cornstarch
or high polyose diet in food-restricted rats (13). Naloxone
failed to reduce the consumption of nonpreferred diets in rats
stimulated to eat by deprivation or injection of NPY but was
extraordinarily potent in reducing intake of preferred foods
(10). Naltrexone, a longer-lasting opiate antagonist, decreased
intake of carbohydrate and fat diets when injected into the
paraventricular nucleus but selectively decreased intake of
preferred diets when injected into the central nucleus of the
amygdala (14). The amygdala, an area involved in pleasure,
may participate in the integration of autonomic, gustatory and
hedonic signals initiated by sucrose ingestion.

Neurochemical changes. Ingestion of sugars can result in
neurochemical changes in brain regions involved in reward
(15–17). The provision of a 25% glucose solution together
with laboratory diet for 12 h each day, followed by 12 h of
deprivation, led to increased binding to dopamine D-1 recep-
tors in the nucleus accumbens shell and core after 30 d. Binding to the dopamine transporter increased in the mid-
brain. Opioid mu-1 receptor binding also increased in several
brain nuclei including the cingulate cortex, hippocampus,
accumbens shell and locus ceruleus. Further, behaviors often
associated with opiate withdrawal were noted after naloxone
was injected in 30-d glucose–cycled rats (15). Naloxone ele-
or the levels of the early gene transcription factor, c-Fos, in
the central nucleus of the amygdala of rats after 3 wk of 10%
sucrose ingestion (17).

A diet high in fat and sucrose has been shown to increase
gene expression of the opioid dynorphin in the arcuate nucleus
(18). However this diet had no effect on gene expression of
another orexigenic peptide, NPY (18). Opioid activity appears
to be affected by the intake of palatable and rewarding foods.

Taste preferences. Naloxone is particularly effective in
reducing the intake of pleasant-tasting fluids (19). These
effects appear to be taste mediated because naloxone injections
blocked the intake of a 10% sucrose solution in sham-drinking
rats (20). The drinking pattern of naloxone-injected rats re-
sembled that seen for 5% sucrose solutions (21), suggesting a
change in the perceived hedonic tone of sucrose. Naltrexone
also decreased the positive hedonic properties of sucrose solu-
tions in rats as measured with the taste reactivity test (22).
Opiate blockade does not affect the perception of sweetness in
humans or rats (23,24). Humans report that the pleasantness
of a sucrose solution is diminished after naltrexone adminis-
tration (25–27).

Opiates may also affect the development of sweet taste
preferences. The acquisition of preferences for saccharin was
diminished by the daily pretest administration of naloxone
(28). A peripheral infusion of naltrexone inhibited the rede-
velopment of a preference for a high sucrose diet after a period
of abstinence (29). The consumption of a 10% sucrose solu-
tion was influenced by endogenous opioids as early as 10 d
postnatally (30). Shide and Blass (31) reported that the de-
velopment of a conditioned preference for orange odor paired
with intraoral sucrose infusion in 6-d-old rats was blocked by
naloxone administration.

Palatability and substance abuse

Several studies have linked taste and food preferences with
drug-seeking behavior. In some cases, the pattern of prefer-
ences predicted drug self-administration; elsewhere concurrent
availability of palatable foods or fluids successfully reduced
drug intake. These findings may be related to the actions of
both foods and drugs on a common substrate, the mesolimbic
dopaminergic system. Many drugs of abuse cause an increase in
dopamine release in the nucleus accumbens. Similarly, the
ingestion of sucrose and other palatable foods has been shown
to cause an increase in dopamine release (32,33).

Psychostimulants and opiates. When rats are provided
with a palatable solution of glucose and saccharin concurrently
with intravenous cocaine, cocaine self-administration is re-
duced (34). Likewise, oral consumption of amphetamine is
reduced by access to dietary sucrose or fat (35). In other
studies, the acquisition of drug-seeking behavior was more
rapid in rats with a high sucrose intake at baseline than in rats
with a low sucrose intake. In contrast, no relationship was
observed between fat intake and subsequent cocaine self-
administration (36), or between saccharin intake and cocaine
(37,38), at least not in male rats (39).

Most research on dietary preferences and opiate intake has
dealt with the intake of sweet substances. Rats self-adminis-
tered less of the opiate etonitazene when a glucose-saccharin
solution was present than when it was absent (40). Outbred
rats selected for high saccharin intake self-administered more
morphine than rats selected for low saccharin intake (41). In
contrast, rats selectively bred for high or low saccharin intake
did not differ in the acquisition of heroin self-administration
(39). In another study, dietary fat consumption at baseline was
predictive of subsequent intakes of an 0.8 g of morphine/L
solution (42).

In humans, heroin and/or methadone users report an in-
creased intake of sugar (43,44). In measures of subjects in a
methadone maintenance program, increased appetite for
sugar/sweets was reported during methadone maintenance and
when “street using” (45). Introspective and retrospective re-
ports of incarcerated drug users (mostly heroin users) suggest
that greater craving for sweets was experienced before than
after taking the drug (46). Higher sugar consumption may be
either a consequence of prolonged opiate use or an attempt to
substitute for the drug when it is not readily available.

Ethanol. The intake of ethanol is reduced by the concur-
rent availability of sugar, fat and saccharin solution (47). In
outbred rats and in lines of rats selectively bred for high or low
ethanol intake, positive relationships have been observed be-
 tween the intake of saccharin or sucrose and the intake of
ethanol (37, 48, 49). Female rats selectively bred for high alcohol intake (AA rats) consumed more dietary fat than rats bred for low ethanol intake (ANA rats) (50). In AA rats, ethanol intake was negatively correlated with carbohydrate intake and positively correlated with protein intake. In other studies (51), rats selected for high fat preference consumed more ethanol than rats selected for high carbohydrate preference. However, not all those studies have been replicated (50, 51). Using different lines of alcohol-prefering and non-alcohol-prefering rats, Prasad et al. (52) reported that the alcohol-prefering rats consumed less carbohydrate and more protein than the non–alcohol-prefering counterparts. In outbred rats, no relationships were observed between diet preferences and ethanol intake. Although several studies point to a relationship between sweet preference and ethanol intake, the relationship between fat and ethanol intake is unclear.

In newly sober outpatients, the duration of sobriety was associated with increased sugar use in beverages (53). Taste preference test conducted with recently detoxified alcoholics showed that a greater percentage preferred more intense sucrose solutions compared with nonalcoholic controls (54). A family history of alcoholism was also associated with increased preference for concentrated sucrose solutions (54). However, other studies have failed to link sweet taste preferences with alcoholic status or a family history of alcoholism (55, 56).

**Neuropeptides and energy expenditure**

Diet composition may lead to changes in neuropeptides within brain nuclei regulating energy metabolism. A low fat diet enhanced NPY gene expression in the arcuate nucleus relative to a low carbohydrate diet (57). Sucrose feeding suppressed adrenalectomy-induced increases in corticotrophin-releasing hormone gene expression in the hypothalamic paraventricular nucleus and the central nucleus of the amygdala (58). The intestinal content of enterostatin, which is produced in the intestine but has central sites of action, was increased by a high fat diet (59).

Manipulations that influence feeding behavior may also affect energy expenditure. Increased NPY gene expression after low fat feeding was accompanied by a marked decrease in the expression of uncoupling protein 1 (UCP1) in brown adipose tissue, suggestive of reduced capacity for thermogenesis (60). NPY decreases UCP1 activity in brown adipose tissue (61). Bray et al. (62, 63) demonstrated that several regulatory neuropeptides affect the activity of the sympathetic nervous system. Corticotrophin-releasing hormone, glucagon and enterostatin, all of which decrease feeding, result in activation of the sympathetic nervous system (64–66), whereas NPY, β-endorphin and galanin, all of which promote feeding, reduce sympathetic nerve activity (67, 68). To date, the five UCPs that have been identified all have the capability to uncouple oxidative phosphorylation from ATP synthesis and therefore decrease the efficiency of energy utilization (69). Any changes in thermogenic potential by UCP may influence energy balance and therefore increase the propensity to gain body weight (70).

UCP1 is located primarily in brown adipose tissue. UCP2 expression is most pronounced in white adipose tissue, and UCP3 is highly concentrated in muscle (69). UCP4 and UCP5 (also known as brain mitochondrial protein) are located primarily in brain (71). Studies have shown that high fat feeding increases the expression of UCP1, UCP2 and UCP3, with the direction of change being specific for separate tissue deposits (72–74). Our recent study showed that sucrose feeding for 2 wk led to an elevated UCP3 gene expression in muscle and to decreased energy efficiency, suggesting that sucrose effects on energy balance may be mediated by UCP3 (75). Free fatty acids have also been shown to induce the UCP3 gene (74).

Dietary manipulations may influence energy expenditure through changes in central neuropeptide activity. Several regulatory neuropeptides at multiple brain sites influence the expression of the UCPs. Data from our laboratory indicate that NPY, cocaine-amphetamine–related transcript, leptin and urocortin all influenced gene expression of UCP1, UCP2 and UCP3 (61, 76–79). These changes in UCP gene expression may be indicative of changes in the thermogenic potential of adipose tissue.

The impact of regulatory neuropeptides on energy intakes is, for the most part, directly linked to food preferences. Fat and sugar are among the most highly palatable and most preferred foods. Sustained fat and sugar consumption affects neural circuitry in a number of brain areas involved in appetite, reward and energy metabolism. Because many of the brain sites involved in feeding behavior are also important in drug seeking, the ingestion of fats and sugars may affect the self-administration of drugs of abuse. A better understanding of regulatory neuropeptides may aid in the design of improved programs for drug abuse prevention and treatment.

**LITERATURE CITED**