The Effects of Benzodiazepines on Feeding Behavior

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Abstract

In addition to their anxiolytic effects, benzodiazepines also increase food consumption in both rats and in humans. It was originally thought that the increase in feeding behaviors produced by benzodiazepines was caused by the drugs’ anxiolytic effects. Early research in the field seemed to support this hypothesis, but more recent experiments raise questions that cannot be explained by the removal of anxiety hypothesis. Benzodiazepines increase stimulus consumption of appetitive stimuli in both stressful and non-stressful environments, so the changes in feeding behavior produced by benzodiazepines cannot be attributed solely to the drugs’ anxiolytic properties. Many studies have indicated that the change in feeding behavior may be due to a benzodiazepine-mediated change in palatability of the stimulus caused by benzodiazepines rather than their anxiolytic effects.

Several methods have been developed to study changes in palatability of stimuli, and these methods have been used to study the effects of benzodiazepines on feeding behavior. Consumption patterns, taste reactivity tests, and micro-structural analysis of licking behavior each have advantages and disadvantages in the study of palatability. This paper will explore those methods and the studies that have contributed to the study of the taste-mediated increase in food consumption caused by benzodiazepines.
Introduction

Benzodiazepines are used in clinical settings as mild sedatives and as anxiolytics. They were developed in the 1960s as an alternative to barbiturates, which have a high potential for abuse and addiction and as well a high potential for overdose. Both drug classes depress the central nervous system, causing their sedative effect, but benzodiazepines have less of a sedative effect especially on brain areas that control respiration than do barbiturates. It is only at very high doses that they repress respiration, making their overdose potential much lower.

Bretazenil, chlordiazepoxide (CDP), midazolam, and lorazepam (Valium) are among the many benzodiazepine agonists developed to have these effects. They all have their effects on GABA receptors, though the particular sites of action of benzodiazepines remain to be found. Benzodiazepine agonists are substances that have an affinity for, or bind to, benzodiazepine-specific GABA receptors to produce a biological change. Partial agonists also have an affinity for benzodiazepine receptors, but they do not have the efficacy of full agonists; they may produce some but not all of the behavioral effects that agonists do. Benzodiazepine antagonists have an affinity for benzodiazepine receptors but no efficacy; they do not cause any biological changes themselves but simply block agonists from causing a response.

Bretazenil was created as an anti-anxiety drug in 1988 but was never marketed for commercial use. It is a partial benzodiazepine agonist; it binds with the same affinity to benzodiazepine receptors, but does not have the full efficacy of benzodiazepines. Chlordiazepoxide (CDP), marketed as Librium, has a medium to long half-life and has full efficacy and affinity at benzodiazepine receptors. CDP is used to treat anxiety disorders and to treat the symptoms of alcoholism, and it is sometimes used to alleviate anxiety before surgical procedures. It is available in an oral form. Midazolam, too, is used as a pre-operative anxiolytic.
It has a much shorter half-life than other benzodiazepines and is administered intravenously or intramuscularly. Midazolam is generally used as a sedative given both before and during surgical procedures.

These drugs all act on benzodiazepine-specific receptors on GABA neurons in the brain. The presence of benzodiazepine receptors indicates that there are endogenous benzodiazepines that control behavior, particularly anxiety and stress responses; as yet, these endogenous benzodiazepines have not been identified.

An unexpected effect of benzodiazepines is their ability to increase feeding behavior. Patients who use benzodiazepines usually report weight gain as a side effect. The hyperphagic effects of benzodiazepines were originally attributed to the anxiolytic effects of the drug class. Testing procedures that have aversive components (i.e. injections, shock, novel environments) may make animals feel anxious, and their anxiety may reduce their consumption of food or solutions. The anxiolytic hypothesis explains the increased feeding behavior as a decrease in this anxiety; benzodiazepines decrease the anxiety animals feel during aversive testing procedures, so that animals will eat when they normally would be too afraid to do so (Berridge and Treit, 1986).

More recent studies have shown that the benzodiazepine-induced hyperphagia is more likely caused by a change in the palatability of foods and not the anxiolytic effects of the drug. Benzodiazepines increase feeding behaviors under non-stressful and stressful conditions alike, which indicates that benzodiazepine-induced feeding is not dependent on a reduction of anxiety (Peciña and Berridge, 1996). Instead, the behavior is more likely to come from a change in palatability that specifically enhances the hedonic palatability of food (Cooper 1980).

Several methods have been used to study the effects of benzodiazepines on feeding behavior. Experiments designed to measure consumption patterns are particularly prevalent in
earlier periods of research. These studies focused on intake and consumption patterns to develop a concept of feeding in the rat and how benzodiazepines affect stereotypical feeding behaviors. Preference tests are also used to measure consumption patterns. In a two-bottle preference test, two stimuli are presented together, and the subject can choose which solution to drink. The amount of each stimulus consumed is an indication of preference and may be reflective of increased palatability as well.

More recently another methodological form has emerged in the research on benzodiazepines and feeding behavior. Microanalysis of licking behavior to various tastants allow the researcher to separate orosensory responses and palatability from post-ingestional responses that affect behavior according to caloric content, nutritional value, or satiety. Though measures of licking behavior appear less often in the literature at this point in time, this will likely become one of the leading and most effective methods of examining palatability in the future. This review will discuss these different procedures used to study the taste-mediated effects of benzodiazepines on feeding behavior.
Consumption Patterns

The earliest research studies in this field were designed to study consumption patterns in rats after treatment with benzodiazepines. Consumption patterns are generally measured through intake and preference tests. Though these studies have used very different approaches, the result is typically the same: benzodiazepines increase the palatability of appetitive or neutral stimuli but do not have much effect on the consumption of aversive stimuli.

Substance intake is one of the variables measured most often when studying benzodiazepine-altered feeding behavior. Meal size is an accurate measure of feeding response and simple intake measurements have been used to determine the basic effects of benzodiazepines on eating behavior: benzodiazepines cause the subject to eat more.

Clifton and Cooper (1996) measured the effects of bretazenil, a partial benzodiazepine agonist, to confirm that benzodiazepines produce a strong hyperphagic response. Rats treated with bretazenil in this experiment nearly doubled the size of their first meal after treatment. In addition, the benzodiazepine agonist ZK93426 blocked this hyperphagic effect and reduced the rats’ intake of water during the first two hours of the test. Increased intake particularly occurred in the first meal after the drug treatment.

Though meal size is a good measure of the basic effects of benzodiazepines on feeding behavior, it is important to discriminate whether the increase is caused by a drive to satiate hunger or by a drive to eat because a food is more palatable. Though Clifton and Cooper (1996) described an increase in food consumption after the administration of benzodiazepines, it was unclear from their study if benzodiazepines were causing the animal to be hungrier or if benzodiazepines were causing foods to taste better.
Meal pattern analysis is a method used to specify the motivations behind feeding behavior. This type of analysis allows researchers to characterize specific feeding patterns and to examine satiety sequences in order to determine whether it is the anxiolytic effects of benzodiazepines that cause increased feeding behaviors or a benzodiazepine-mediated change in palatability. Following ingestion, rats will display a stereotypical sequence of behaviors consisting of exploration, grooming, and sleep. Changes in these sequences can indicate that a drug is having an effect on ingestional behavior, and specific changes in meal patterns indicate the cause of the change.

Several variables are measured in meal pattern analysis to determine motivation. First, the animal’s responses are divided into feeding bouts. A bout is defined as a particular amount of time, determined by the researcher, during which the animal eats but performs little or no alternative behavior such as grooming or exploration. The amount of time that passes in between each feeding bout is called the intrabout interval. Changes in the duration of a feeding bout can indicate palatability. Short bout durations indicate that the animal is feeding to become sated; the food may not be particularly pleasing, but the animal eats because it is hungry. An increase in bout duration, however, indicates an increase in palatability: the animal sustains its eating behavior for a longer period of time because the food tastes better. Wiepkema (1971) was one of the first researchers to explain the increase in the duration of feeding bouts as an indicator of palatability.

A micro-analysis of meal patterns has shown that midazolam, a short-acting benzodiazepine, enhances the duration but not the frequency of feeding bouts of appetitive stimuli (Cooper & Yerbury 1986). In this study, non-deprived rats, when given high doses of midazolam, increased the duration of feeding but did not increase their frequency. Had the bout
frequency increased, one could suspect that the change in behavior was due to the rats’ increased hunger; however, the increase in bout duration is likely due to a change in palatability.

Cooper (1987), too, found that rats presented with saccharin-flavored mash in a saccharin-, quinine-, or unadulterated preference test not only lengthened feeding bouts after they were given CDP but also increased total consumption of food; similar to the 1986 experiment and to Wiepkema’s results, the number of feeding bouts was not affected by CDP, only the duration. The increase in the length of feeding bouts, not their number, is indicative of a benzodiazepine-mediated change in palatability, not hunger or satiety.

Benzodiazepines also decrease the initial latency before feeding, a result that is as yet an anomaly in the research on benzodiazepines and feeding. Initial latency is defined as the period before a food or solution is sampled for the first time. Though it is a useful measure of the effects of benzodiazepines, latency does not indicate a change in palatability (Cooper and Francis, 1979, 1980) because latency occurs before the animal has tasted a food or solution—before it has made a decision about palatability at all. A decrease in latency more likely corresponds with the hunger and satiety hypothesis of benzodiazepine effects: the amount of time an animal takes before eating is decreased because it is hungry. However, even non-deprived rats have shown this decrease in initial latency. These results suggest that a change in palatability may not be responsible for all of the changes in feeding produced by benzodiazepines. The drugs may have their effects in several different systems, including those that control palatability and natural reward as well as those that control hunger and satiety.

Preference tests are a second type of measurement of consumption patterns. Two-bottle preference tests are accurate measures of palatability because the consumption of one solution or one food over another clearly indicates a specific preference for that substance. If a substance is
preferred, it is more palatable. In preference tests, also called choice tests, three factors interact: the type of taste stimulus, the type of behavioral response, and the type of drug being used (Cooper and Barber, 1992).

Solutions with low concentrations of sodium chloride (NaCl) can act as appetitive stimuli, especially when an animal is salt deprived; however, as the concentration of NaCl is increased, the stimulus becomes more aversive. Cooper and Barber (1992) tested bretazenil, a benzodiazepine agonist, and Ro15-4513, a partial benzodiazepine inverse agonist and their effects on salt preference and aversion. Benzodiazepine inverse agonists are substances that bind to the benzodiazepine-GABA receptors but exert the opposite effect of an agonist, so one would expect to see the opposite of benzodiazepine effects, or a decrease in feeding behavior, after administration of Ro 15-4513.

Cooper and Barber used two stimuli in this experiment: a .9 percent salt solution that is usually considered palatable, and a 1.8 percent salt solution, usually considered aversive. Bretazenil selectively enhanced licking to the .9 percent salt solution and even caused the animals to prefer NaCl solutions over water. As previous studies (Berridge and Treit, 1986) have shown, though, the drug did not reduce a relative aversion to the much more potent and aversive 1.8 percent salt solution. The inverse agonist Ro 15-4513 reduced fluid consumption overall but did not reduce the preference for the .9% solution. Both the agonist bretazenil and the partial inverse agonist Ro 15-4513 affected consumption patterns of the preferred solution (.9% NaCl). Bretazenil increased its consumption while Ro-15-4513 decreased it. However, neither agonist nor antagonist reduced the aversion to the stronger solution. By determining the effects of the partial inverse agonist, Cooper and Barber confirmed that benzodiazepines increase consumption of appetitive stimuli but have no effect on aversive stimuli.
Unlike salty solutions, sweet stimuli are almost always appetitive, and in preference tests rats will choose to drink more of a sweet solution than water. Cooper and Greenwood (1992) tested the effects of abecarnil, a β-carboline and benzodiazepine agonist, on salt and saccharin preferences in rats. Abecarnil does not have all of the secondary effects of typical benzodiazepines; it produces fewer signs of sedation and is less addictive than other benzodiazepines, and so it has been considered by some to be only a partial agonist. However, because of these partial effects, abecarnil has been useful in identifying GABA receptors as those responsible for the drug’s effects on food intake and taste preference.

Rats that received injections of abecarnil in this experiment significantly increased their intake of an isotonic (.9%) NaCl solution, confirming the results of Cooper and Barber (1992) who tested the effects of bretazenil. It is important to note that in both experiments, consumption of water in the two-bottle preference tests was unaffected. This result indicates that the effects of benzodiazepines on feeding behavior are selective and depend on palatability.

Rats injected with saline in the Cooper and Greenwood experiment displayed high baseline levels of consumption of saccharin, not an unusual result with a naturally appetitive stimuli. Abecarnil, however, further increased the rats’ consumption of both a saccharin-infused mash and solution. These results show a marked hyperphagic effect of abecarnil even though rats were already consuming large amounts of saccharin in the control group. This indicates that abecarnil has the same effects as classic benzodiazepine receptor agonists on feeding behaviors and taste preferences even though it may have only a selective action on receptors. Research relating the β-carboline abecarnil to benzodiazepines may lead to the development of β-carbolines as anti-anxiety drugs in the future.
In an interesting variation of a preference test, Linda Parker (1989) used taste aversions to study benzodiazepine effects on aversive stimuli. Parker paired lithium-chloride, amphetamine, and saline injections with the presentation of a saccharin solution. Injections of lithium-chloride typically make animals very ill, so when lithium is paired with a particular taste that flavor typically becomes aversive. Animals will avoid that taste in the future because it is linked to the memory of becoming ill. The flavor becomes a conditioned stimulus that precedes sickness, which changes the preference for and the response to that stimulus, a change that is called a conditioned taste aversion.

Though lithium-chloride produces conditioned taste aversions in rats, amphetamine injections do not. When amphetamine is paired with a particular flavor, the flavor does not become distasteful to the rat, indicating that amphetamine-based CTAs function differently than do lithium-based CTAs and are not dependent upon palatability as much as a feeling of eminent danger.

In Parker’s experiment, rats were conditioned with a saccharin solution and then injected with either \textit{d}-amphetamine, lithium-chloride, or saline. Injections of CDP after conditioned taste aversions enhanced saccharin consumption regardless of its conditioned properties. Rats consumed more saccharin solution after being injected with CDP than they did without, indicating that CDP enhances the palatability of solutions that are conditionally distasteful (lithium-paired) as well as those that are not (saline- or amphetamine-paired). These results confirmed those like Berridge and Treit (1986) and Cooper (1989) whose results support the palatability hypothesis. It also offers a base for future research on learned taste preferences, which could be helpful in treating patients with severe taste aversions, as those that occur during chemotherapy treatments.
When measuring the preference between two or more solid foods, it is difficult to separate taste aspects from other variables such as texture, caloric density, and nutrient content. Cooper (1987) has taken steps to eliminate these different variables and to isolate taste as the only dependent variable to be measured. Using wet mash as a base, saccharin or quinine was added to create three taste stimuli. Preference tests showed a particular preference for the saccharine-flavored mash that varied depending on the dose of CDP (0, 5, or 10 mg/kg). Preference for the unadulterated mash was not affected, nor was preference for the quinine-flavored food. These results again confirm Berridge and Treit’s (1986) findings that benzodiazepines increase the preference for appetitive stimuli but do not increase or decrease responses to neutral or aversive stimuli.

Both meal pattern analysis and preference tests suggest that benzodiazepines are likely acting in the taste nucleus to cause the benzodiazepine-mediated increase in feeding behavior. Benzodiazepines increase feeding specifically by increasing the duration of feeding bouts, not by increasing the number of feeding bouts. Preference tests indicate that rats given benzodiazepines increase baseline consumption of appetitive stimuli. Behavioral responses to aversive stimuli, which are biologically resistant to change, are largely unaltered by the drug class. However, consumption patterns are not specific enough to dispel the possibility that hunger and satiety mechanisms are working as well. Taste reactivity tests eliminate measures of post-ingestive stimuli that control hunger and society and measure only palatability, which make them an effective method for examining the palatability hypothesis.
Taste Reactivity

Because feeding consists of a number of behaviors with complex controls, it is difficult to use ingestive measures completely confidently in determining the anxiolytic properties of drugs. Though preference tests can be somewhat useful in measuring palatability, taste reactivity studies are even more useful. In taste reactivity tests, tastants are infused directly into the rat’s mouth through a previously implanted cannula. The rat’s reactions to each stimulus can then be recorded by counting the number of ingestive or positive hedonic reactions versus the number of aversive reactions. These behaviors are highly sensitive to the palatability of a substance. (Berridge and Treit 1985). Because taste-elicited facial responses do not require knowledge of the subjective state of the animal, taste-reactivity studies are more accurate in defending the palatability hypothesis than intake or preference tests.

The taste reactivity test was developed by Grill and Norgren (1978). It measures palatability by scoring the number of affective and aversive reactions to a stimulus infused into the mouth according to species-specific feeding behaviors. In most of the work in the field, and in the research that will be discussed here, rats have been used as the primary subjects. Therefore, the types of reactions are scored according to normal reactions made by rats to specific stimuli. Positive hedonic reactions include tongue protrusions, lateral tongue protrusions, and, in cases where a solution is not infused by a cannula, paw licking. Aversive responses include: gapes, defined as a wide opening of the mouth; chin rubs, defined as bringing the mouth in contact with the floor; face washing; forelimb flails; paw treading; and head shakes. These actions are typically videotaped, then replayed frame-by-frame to provide a quantitative measurement of behavior. The number of aversive reactions is compared to the number of
positive hedonic reactions to obtain a score that corresponds well with palatability (Söderpalm and Berridge, 2000).

Berridge and Treit (1985) studied taste reactivity responses to infused sucrose, HCl, and quinine. They found that after injection with CDP, the number of ingestive, positive reactions to all three of the tastes was increased. There were significantly more positive reactions to sucrose in the CDP condition than in the saline condition. Aversive reactions to sucrose were not significantly affected. CDP caused a decrease in aversive forelimb flails and an increase in ingestive behavior when the rat’s mouth was infused with HCl, a sour stimulus. Similarly, when the rats tasted quinine, a bitter and particularly aversive stimulus, positive responding increased but aversive responses remained unchanged. These data support the palatability hypothesis explained by Berridge and Treit (1986).

Abecarnil is a benzodiazepine agonist that has been studied using preference tests (Cooper and Greenwood, 1992) as well as taste reactivity tests. As mentioned before, consumption of .9% NaCl solution was increased when rats were first injected with abecarnil (Cooper and Greenwood, 1992). Similarly, abecarnil increased appetitive taste responses to a 3% sucrose solution in an experiment by Cooper and Ridley (2005). When viewed together, these studies demonstrate that not only do abecarnil and other benzodiazepines cause an increase in feeding behaviors for relatively appetitive solutions, salty or sweet, but also that the increase is due to an increase in palatability.

Taste reactivity studies have also been conducted using opiate-antagonists. Opiates and benzodiazepines both increase food intake and increase hedonic responses to sweet tastants. Therefore, it can be speculated that the two drug classes share a mechanism of action in the control of feeding behavior. Administration of diazepam nearly doubled positive hedonic
reactions to a bittersweet (sucrose-quinine) solution. However, when naltrexone, an opiate-antagonist, was administered before diazepam, naltrexone completely blocked the enhancement of positive reactions caused by diazepam and disrupted the reduction of aversive taste reactions normally caused by benzodiazepines (Richardson, 2005). The author of the study argues that endogenous opioid neurotransmitters may be critical to the benzodiazepine-induced enhancement of hedonic liking and may function in a system of natural taste reward. However, another hypothesis may better explain these results. Taste reactivity tests examine very small behavioral responses. Opioid antagonists block responses in the natural reward system and block pleasure responses. Benzodiazepines may still increase palatability even when opiate receptors are blocked, but pleasurable reactions may not occur because the reward system is not functioning. Opiates may affect the behavioral responses to taste stimuli, but they may not be involved with the mediation of palatability.

A disadvantage of most taste reactivity tests is the invasiveness of the procedure. In order to study infused solutions, a cannula must be surgically implanted into the subject’s mouth. Gray and Cooper (1995) developed a method that combines elements of both intake measures and taste reactivity by examining voluntary response to solid or semi-solid foods. No cannula is involved in this procedure; subjects choose to sample various stimuli. Animals are videotaped as they eat, and their reactions are scored in the same manner as taste reactivity tests. The amount of food consumed can also be measured and added to taste reactivity data to provide a more comprehensive measurement of feeding behavior. Gray and Cooper (1995) used this technique to measure the effects of midazolam on feeding behaviors and found results similar to other studies: midazolam significantly increased intake of a sucrose solution but did not increase intake of a quinine solution. An increase in overall taste responses was observed over all
conditions, and there was a decrease in aversive responses to sucrose by 76%. Aversive responses to sucrose, an appetitive stimulus, are few in number even without administration of a drug. Benzodiazepines typically do not have an effect on aversive responses, especially to aversive stimuli, but because sucrose is an appetitive stimulus, these results probably do not indicate a benzodiazepine effect on aversive responses.

Taste reactivity studies are more reliable than intake patterns are when studying palatability of foods because they do not rely on subjectivity to determine the motivation of the animal. Intake patterns only indicate an increase in feeding behavior. This is helpful in early research when attempts are being made to identify the basic effects of benzodiazepines on feeding behavior, but they do not explain how benzodiazepines produce that change in behavior. Preference tests, on the other hand, can indicate a change in palatability, teasing out the motivation behind increased consumption. If CDP only increases feeding because of its anxiolytic effects, we would expect to see no change in reactions to taste stimuli or, if a change in reactions did occur, both ingestive and aversive actions would be affected. If the effect of CDP on feeding behavior is due to a change in palatability, though, the number of positive hedonic behaviors would increase (Berridge and Treit 1985). This is exactly what taste reactivity studies show.

Taste reactivity studies successfully examine pre-ingestive responses to taste stimuli without being susceptible to post-ingestive effects. Pre-ingestive responses, which occur immediately as the taste stimulus enters the oral cavity, are a good indicator of palatability. Microanalysis of consumption patterns can give some indication of changes in palatability, but after a few minutes into testing, post-ingestional mechanisms begin to drive behavior as well. After the first few minutes, it is very difficult to measure palatability as separate from post-
ingestive mechanisms. Results of taste reactivity studies indicate that benzodiazepine-mediated increases in feeding behaviors are due to an increase in palatability because they increase the number of hedonic responses to appetitive stimuli before post-ingestive mechanisms begin to influence behavior. Meal pattern analysis also supports the palatability hypothesis, indicating that increased food consumption is due to increases in feeding bout duration and not an increase in the number of feeding bouts.

Micro-structural Analysis of Licking Behavior

One of the most recently developed methods of studying the effects of benzodiazepines on feeding behavior is a micro-structural analysis of licking behavior. Very similar to meal pattern analysis, micro-analysis of licking behavior measures the number and patterns of licks to a taste solution rather than to solid foods. It is difficult to change the taste of solid foods without also altering texture and caloric content at the same time. Taste solutions reduce this variability, minimizing the amount of change in texture between stimuli and limiting post-ingestive signals, enabling the researcher to isolate the independent variable, taste.

Tests of licking behavior can be either short-term or long-term, and microanalysis allows the researcher to examine many different aspects of behavior in the same test session. Brief contact tests focus on the initial response to a stimulus, isolating palatability as a variable (Higgs and Cooper, 1996). Long-term tests measure post-ingestive influences in addition to palatability. The many results obtained from long-term tests can confound results if the goal is to isolate palatability as a variable. However, long term tests of licking behavior can provide more thorough information on many aspects of feeding behavior when patterns over a longer period
are analyzed. Micro-structural analysis of licking behavior is one of the newer methods for studying the effects of benzodiazepines on feeding behavior, but it is one of the most successful ones.

Orosensory responses are some of the first to occur during feeding, which is why taste reactivity studies are so successful in measuring the initial response to taste stimuli. This input from the oral cavity then stimulates continued ingestion through positive feedback from the gastrointestinal tract. Later, when the animal is sated, another signal is sent from the GI tract to inhibit feeding. Cooper and Higgs (2005) found that administration of midazolam increased the number of licks but not the number of bouts of licking to salt solutions. Cooper (1987) measured similar responses such as bouts of feeding and meal size in rats with solid food by using meal pattern analysis. Cooper found that rats preferred a saccharine-flavored mash even more after the administration of CDP, but rats’ response to a bitter quinine stimulus and a neutral stimulus were unaffected. The duration of each bout of feeding was lengthened, but the number of bouts did not increase. The intrabout rate, defined as the amount of time between bouts during which the animal was engaging in non-feeding behaviors was also diminished for all concentrations of salt solutions. As the concentration of salt increased, making the solution more aversive, the number of bouts decreased. When CDP was administered, the total number of licks to salt solutions was increased, and the enhancement occurred at the earliest stage of consumption, indicating that palatability was responsible for the change in behavior. This study also showed that the administration of CDP did not have a significant effect on the number of bouts but increased bout duration. This indicates that CDP selectively enhances palatability and maintains ingestive behavior.
Higgs and Cooper (1998) analyzed the microstructure of licking behavior to three stimuli: sucrose; Intralipid, a fat emulsion; and maltodextrin, a non-sweet tasting polysaccharide. They found that as the concentration of sucrose in a solution increased, licking increased both by the total number of licks and the number of bouts of licking. When midazolam was administered, the number of licks to sucrose increased depending on the dose of the drug, but midazolam did not produce an effect on the number of bouts of licking to sucrose. The drug increased the amount of licking to both Intralipid and to maltodextrin. The results of this experiment indicate that the taste-mediated effects of benzodiazepines on feeding behavior can occur with more stimuli than just the four basic tastants that are usually studied.

Inverse agonists are also helpful to determine the specific effects of benzodiazepines. Inverse agonists have the opposite effect of agonists; therefore, inverse agonists of benzodiazepines produce an anorectic effect rather than a hyperphagic effect. In a micro-structural analysis of the ingestion of sucrose and sodium-saccharin solutions over a 20-minute period, Higgs and Cooper (1996) found that Ro 15-4513, a benzodiazepine inverse agonist, produced a severe decrease in the consumption of both saccharin and sucrose solutions. It almost eliminated the consumption of both solutions. Because the test was conducted before post-ingestional signals could influence responding, the anorectic effects of Ro 15-4513 can be attributed to a change in palatability rather than a feedback signal of caloric intake or satiety. This study is consistent with agonist studies because it suggests that inverse agonists decrease consumption as a result of a decrease in palatability.

The microstructure of licking behavior is important to discovering the mode of drug action. At the same time, it is important to have an idea of where benzodiazepines have their
effects in the brain and of which areas are responsible for benzodiazepine-related changes in feeding patterns.

**Possible Sites of Action**

An important area of research that extends beyond palatability tests concerns the site of action of benzodiazepines as they affect feeding behavior. The fourth ventricle has been targeted as a possible site of action of benzodiazepines on feeding behavior. Direct administration of midazolam into the IVth ventricle significantly increased the consumption of a palatable wet mash in non-deprived rats. (Higgs and Cooper 1996). Peciña and Berridge (1996) tested the effects of diazepam in both the lateral and IVth ventricles. They found that low doses of diazepam produced more changes in feeding behavior when injected into the IVth ventricle, but at higher doses the drug had effects when injected in either area.

Higgs and Cooper (1996) have tested the effects of an injection of midazolam into the parabrachial nucleus. By measuring consumption patterns post-injection, they found that the baseline intake of wet mash almost doubled when midazolam was injected into the PBN, but the drug had no effect if placed elsewhere in the brain. Hyperphagia was blocked when the rat was pretreated with flumazenil, a benzodiazepine antagonist, indicating that the PBN could be an important brain area in which benzodiazepines have their effects on feeding. Later research by Söderpalm and Berridge (2000) confirmed the importance of the PBN in the benzodiazepine-mediated increase in intake and demonstrated that other brain sites are probably not responsible for the effects.
Though benzodiazepine receptors are more dense in the forebrain, receptors also exist in the caudal brainstem, making it another possible site of action for changes in feeding behavior. Berridge (1987) examined the influence of the mesencephalon and areas below it on these changes. Rats in the experimental condition had their cerebrums removed at the mesencephalic level, then had a cannula implanted for the infusion of taste stimuli; control animals had only the cannula implanted. When taste reactivity tests were conducted, intact rats did show higher levels of ingestive responses to sucrose, but the mesencephalic decerebrate rats showed the same pattern of responding, if at lower levels, as intact animals when treated with CDP. These results indicate that the benzodiazepine receptors and the important neural circuitry for modulating feeding behavior through benzodiazepines are located within or below the mesencephalon, suggesting brain areas that should be examined in future studies.

Discussion

The three methods discussed here—consumption patterns, taste reactivity tests, and microanalysis of licking behavior—each contribute a different set of knowledge to the study of benzodiazepines and their effects on feeding behavior. Results from all of the studies discussed here confirm that benzodiazepines increase the consumption of appetitive stimuli and do not effect consumption of aversive stimuli. These findings make sense biologically: Aversive stimuli typically indicate something harmful. For example, sour foods can indicate that a food is spoiled or rancid. Poisons typically have a bitter taste, which is why bitter foods are often perceived as aversive. Because they indicate some danger to the animal, these biological interpretations of palatability are more resistant to changes in stress or anxiety than are appetitive stimuli.
Appetitive stimuli signal high nutrient or caloric content for the animal and are not usually a threat to the animal. It is possible that the palatability of appetitive stimuli is more flexible to change than the palatability of aversive stimuli.

Benzodiazepines may be able to ease the unpleasant effects of treatment for cancer patients. Lorazepam is already used as an antiemetic after chemotherapy to ease vomiting. Because benzodiazepines have the ability to increase the palatability of appetitive stimuli, they may be useful in treating cancer patients who develop conditioned taste aversions to many foods. Patients who lose weight during chemotherapy sessions may also benefit from this effect of benzodiazepines because they suffer from a decrease in palatability of foods due to conditioned taste aversions. Many foods come to be paired with sickness when they are eaten after chemotherapy sessions, causing the patient to perceive those foods as less palatable. Benzodiazepines may be distributed in this case to stimulate feeding behaviors and to counteract the effects of those conditioned taste aversions. Linda Parker’s experiment (1989) exploring lithium-paired conditioned taste aversions offers promise to patients in this field, and her research is built upon the results of other experiments that identify benzodiazepines as producing changes in palatability in the taste system rather than just a change in hunger and satiety.

The increase in feeding behavior produced by benzodiazepines often leads to unwanted weight gain in patients who use benzodiazepines as sedatives. The studies discussed here give evidence that this change in behavior is due to the effects of benzodiazepines themselves. Patients should be cautioned of this side effect of benzodiazepines. Obese patients in particular should be warned of the effects of benzodiazepines so that they can closely monitor food intake to avoid future complications to their health.
There is still much research to be conducted on benzodiazepines and feeding behavior, especially using micro-structural analysis of feeding behavior to determine the underlying mechanisms that drive the changes produced by benzodiazepines. Further study in brain areas where benzodiazepines have their effects on feeding will help to identify the mechanisms of those changes as well. Future studies may include injecting benzodiazepines directly into the third and fourth ventricles of the brain or into the hypothalamus. Some studies have already begun to explore the effects of benzodiazepines in the ventricles, but it is also important to determine if benzodiazepines do have an effect on hunger and satiety, regulatory actions that are controlled in the hypothalamus.

Because micro-structural analysis of licking behavior is the most efficient way of isolating palatability, more studies should be done using this method of testing. Short-term testing is the best way to separate post-ingestional responses from changes in palatability. Future studies may include injecting benzodiazepines into specific brain areas and then using micro-analysis of licking behavior to determine what brain areas produce the most change in licking behavior.

Future research should also explore the function and location of endogenous benzodiazepines. By understanding the body’s natural system for managing stress and anxiety, new pharmacology may be developed to treat psychological conditions such as generalized anxiety disorder or post-traumatic stress syndrome, both products of extreme stress and anxiety.
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