GABA-A Receptor Activation Influences Consumption of Appetitive and Aversive Tastants

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Introduction

Benzodiazepines are a class of anxiolytic drugs that facilitate the effectiveness of the GABA neurotransmitter to hyperpolarize cells. Benzodiazepine receptors are broadly distributed throughout the CNS including the gustatory nuclei of the hindbrain, the nucleus of the solitary tract (NST) and the parabrachial nucleus (PBN). Previous research has provided evidence that corticofugal projections utilize GABA in hindbrain gustatory nuclei in order to shape the afferent gustatory signal. GABA agonists appear to narrow the responsiveness of NST gustatory cells to taste stimuli.

Benzodiazepines have a well-documented hyperphagic effect on palatable taste stimuli and foodstuffs. The research suggests that the benzodiazepine-induced consumption is related to an enhancement of the gustatory evaluation of the ingesta. The majority of research has focused on sweet and fat tastants or foodstuffs with little research exploring the ability of benzodiazepines to influence the gustatory evaluation of aversive stimuli such as moderate concentrations of salt, sour, or bitter tastants.

Previously, we have shown that chlordiazepoxide (CDP), the first synthesized benzodiazepine, increased ingestive responses to both appetitive and aversive tastants during brief-access and long-term testing. Our behavioral findings were consistent with CDP-induced alterations in the neural responsiveness to appetitive and aversive stimuli in the PBN.

This study expands upon our previous work by examining the effect of CDP on the ingestive behavioral responses across multiple concentrations of sweet (caloric and non-nutritive), sour, salt, bitter, and umami taste stimuli during long-term testing. We predicted that CDP would selectively affect taste-mediated variables of intake as opposed to variables associated with motivational states across this wide range of taste stimuli and concentrations.

Methods

***Subjects*:** 48 adult male Sprague-Dawley rats.

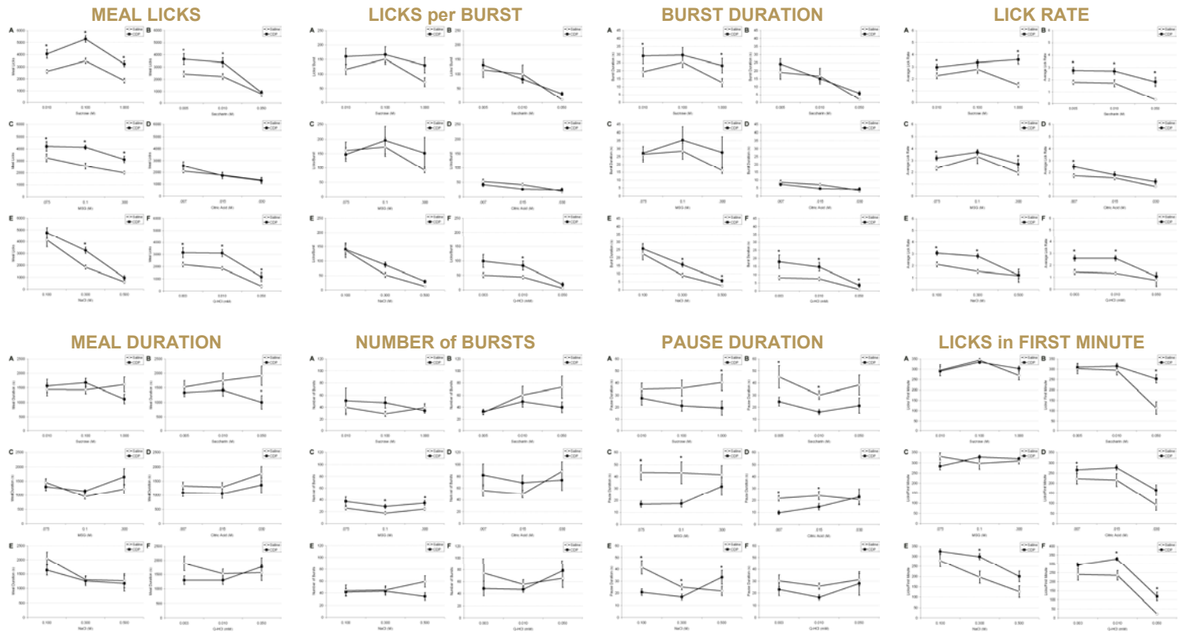
Test Stimuli: Water, sucrose (0.010, 0.1, 1.0 M), saccharin (0.005, 0.01, 0.05 M), MSG (0.075, 0.1, 0.3 M), citric acid (0.007, 0.15, 0.03 M), NaCl (0.1, 0.3, 0.5 M), and Q-HCl (0.003, 0.010, 0.05 mM).

Behavioral Testing Procedures

Three days prior to the experiment, rats were placed and maintained on a 23-hr water restriction schedule. All injections were administered i.p. 20 minutes prior to behavioral testing. Using a counterbalanced design, rats were tested for each taste stimulus on 2 consecutive days with half of the rats receiving a saline injection (150mM NaCl, 1ml/kg) and half of the rats receiving an injection of CDP (chlordiazepoxide, 10mg/ml/kg) on each test day. The rats were divided into three groups (n=16) with each group receiving all tastants within a single concentration group (low, medium, or high). All taste stimuli were mixed daily.

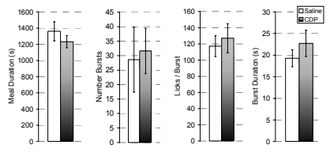
Behavioral tests were daily 60-min sessions in the AC-108 lickometer (DiLog Instruments) in which each lick was recorded. Microanalysis of the data categorized the licking patterns into meals (terminated by 10min pause) and bursts (terminated by 1s pause) of licking.

Data Analysis: All data were statistically analyzed using mixed factorial repeated measures ANOVA and post-hoc paired t-tests (SPSS).

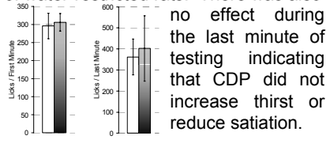


Microanalysis of licking patterns during the first meal of a 60-min, single bottle test following CDP or saline i.p. injection. Licking responses to three concentrations of sucrose (A), saccharin (B), MSG (C), Citric Acid (D), NaCl (E), and quinine-HCl (F) were measured.
In general, there was no effect of CDP on variables associated with motivational state such as: meal duration and number of bursts per meal. In contrast, CDP tended to produce significant effects in variables associated with taste-mediated cues such as meal licks, licks per burst, burst duration, pause duration, lick rate, and licks during the first minute of testing.

MICROANALYSIS OF LICKING TO WATER



Analysis of the licking patterns during testing with water revealed no effect of CDP on variables associated with increased thirst such as meal duration, number of burst, or burst duration. Furthermore, there was no effect of CDP on the number of licks per burst, a variable associated with taste-mediated cues. There was also no effect of CDP on the number of licks during the first minute of testing as might be expected of water-restricted rats. There was also no effect during the last minute of testing indicating that CDP did not increase thirst or reduce satiation.



Results

Meal Analysis:
CDP caused a significant increase in the licks per meal for sucrose, MSG, QHCl, and the appetitive concentrations of saccharin and NaCl. There was no effect of CDP for the sour stimulus, citric acid, at any concentration. In addition, there was no significant difference between the duration of the meals for CDP versus saline. Increased total meal licks with similar meal durations indicates that the temporal licking pattern for the CDP condition must be denser than the saline condition.

Within Meal Analysis:
CDP tended to increase licking to appetitive & aversive stimuli through changes in patterns of licking associated with taste-mediated cues. The number of licks per burst and burst duration increased while the time spend not licking within a burst (pause) decreased. Both lick rate and first minute licks are considered taste-mediated variables because rats can lick faster to more palatable solutions and first minute licks are not governed by post-ingestive feedback. CDP significantly increased the lick rate for both appetitive and aversive tastants and increased the licks in the first minute for aversive stimuli (appetitive stimuli showed ceiling effects for first minute licks).

Conclusions

Despite the general sedative nature of benzodiazepines, our results confirm previous research findings that CDP increases consumption of appetitive stimuli (sucrose) by showing similar effects on non-nutritive sweet and umami. Our results extend previous findings by showing that CDP also acts to increase the acceptance of normally aversive stimuli such as hypertonic salt and bitter. Microanalysis of licking patterns during the meals indicate that CDP is acting primarily through taste-mediated cues as opposed to variables associated with motivational-state cues such as thirst. Our behavioral findings support concurrent electrophysiological recordings of taste-responsive cells in the PBN which suggest that CDP suppresses responses to aversive stimuli and increases the proportion of cells responsive to sweet and salt stimuli.

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