Benzodiazepines Selectively Increase Brief-Access Licking for Gustatory Stimuli Independent of Influences on Motivational State

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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). Benzodiazepines have a well-documented hyperphagic effect on palatable taste stimuli and foodstuffs. Other 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.

Previously, we have shown that chlordiazepoxide (CDP), the first synthesized benzodiazepine, increased ingestive responses to both accepted and aversive tastants during long-term tests (1hr), primarily through changes in licking patterns associated with hedonic taste evaluation with no effect on feeding behaviors associated with postingestive feedback. These behavioral findings were consistent with our previous reports of CDP-induced alterations in the neural responsiveness to sweet, salty, sour, and bitter taste stimuli in the PBN.

This study expands upon our previous work by examining the effect of benzodiazepine (chlordiazepoxide, CDP) and non-benzodiazepine (buspirone, BUS) anxiolytic drugs on the ingestive behavior of rats to a wide range of orosensory stimuli across multiple concentrations during brief-access (15s) trials. Buspirone produces anxiolytic effects as a partial 5-HT_{1A} receptor agonist and thus, we can use buspirone to compare general anxiolytic effects on ingestive behavior to benzodiazepine-specific effects on ingestive behavior. Furthermore, we are expanding our test stimuli to include an aversive, non-gustatory stimulus, capsaicin, in order to assess the effect of anxiolytic drugs on taste-specific ingestive behavior versus general avoidance ingestive behavior.

Methods

***Subjects*:** Adult male Sprague-Dawley rats (CDP: n=16; BUS: n=12)

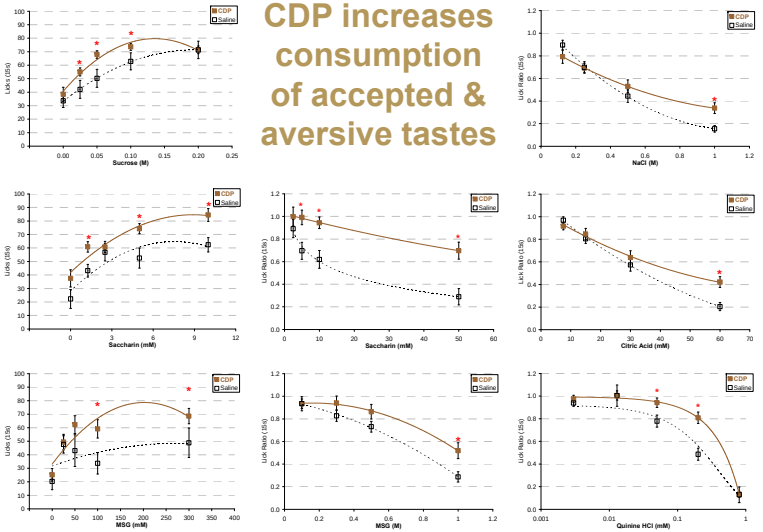
Test Stimuli: Water, sucrose, saccharin, MSG, NaCl, citric acid, Q-HCl, and capsaicin (see figures for specific concentrations).

Behavioral Testing Procedures: Three days prior to the experiment, rats were placed and maintained on a 23-hr water restriction schedule and trained to lick to water presentations in the MS-160 gustometer (DiLog Instruments). During testing, rats were placed on 23-hr water restriction or ad lib water (replete) 24-hr prior to specific tastant test sessions. All injections were administered i.p. 20 min 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 a drug injection (EXP1: chlordiazepoxide CDP, 10mg/1ml/kg or EXP2: buspirone BUS, 1.5mg/1ml/kg) on each test day. All taste stimuli were mixed daily.

Behavioral tests were daily sessions in the MS-160 gustometer in which each lick and the latency until the first lick were recorded. Each test session contained 5 blocks of 4 test stimuli plus water for a total 25 trials. There were 10s intervals between trials and per trial, rats had 30s to initiate a lick followed by a 15s trial duration after the first lick.

Data Analysis: All data were statistically analyzed using repeated measures ANOVA and Bonferroni post-hoc paired t-tests (p<0.05, SPSS).

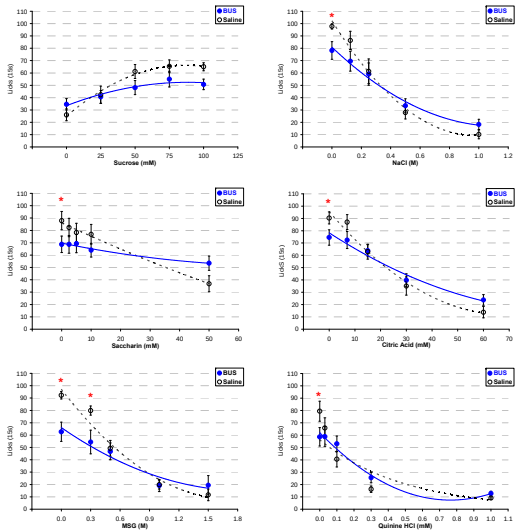
CDP increases consumption of accepted & aversive tastes



ABOVE: The number of licks (15s trials) to normally accepted tastants (sucrose, saccharin, MSG) during water-replete motivation

ABOVE: Lick ratios *(Licks to Tastant / Licks to Water; 15s trials)* to normally aversive tastants (saccharin, MSG, NaCl, citric acid, quinine-HCl) during water-restricted motivation

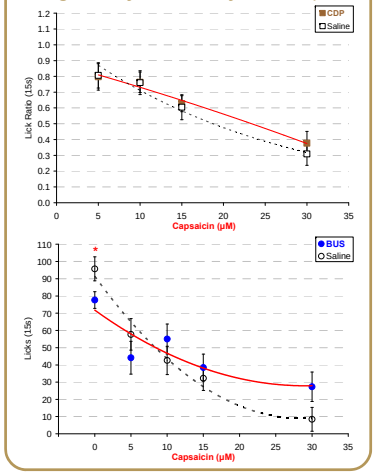
Repeated measures ANOVA revealed significant drug effects compared to saline, stars indicate significant drug effects at specific concentrations (Bonferroni post-hoc, p<0.05).



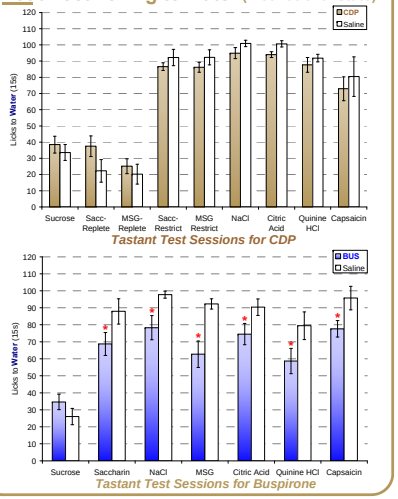
Buspirone(BUS) has no effect on licking to normally accepted tastants (sucrose; water-replete motivation) or normally aversive tastants (saccharin, MSG, NaCl, citric acid, quinine-HCl; water-restricted motivation).

Repeated measures ANOVA revealed no drug effects for tastants, stars indicate significant decreases in licking to water for buspirone compared to saline (Bonferroni post-hoc, p<0.05).

Benzodiazepines do not affect licking to capsaicin (aversive, non-gustatory, orosensory stimulus).



Unlike buspirone, benzodiazepines do not affect licking to water (motivational state).



Conclusions

- CDP uniformly increased licking across taste categories: sweet, umami, salt, sour & bitter with no effect on generalized avoidance of capsaicin (trigeminal stimulus).
- CDP did not affect licking to water during replete or restricted motivational states.
- Buspirone did not affect licking guided by taste cues.
- In absence of taste cues, the anxiolytic effects of buspirone reduced licking to water during the water-restricted motivational state.

Benzodiazepines appear to selectively enhance the hedonic acceptance of all taste categories, independent of motivational states such as thirst, appetite, or general anxiolytic effects.

Acknowledgements

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