Designer Receptors Exclusively Activated by Designer Drugs (DREADD) Inactivation of Forebrain Inputs to the Parabrachial Nucleus in Rats Reveals Dissociable Contributions to Benzodiazepine Hyperphagia in Rats

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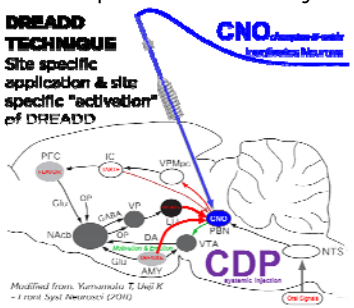
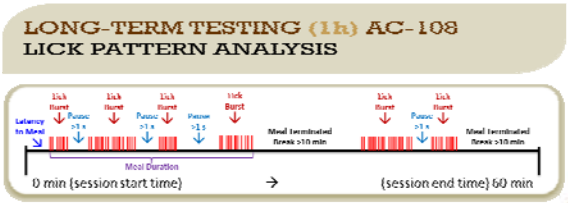
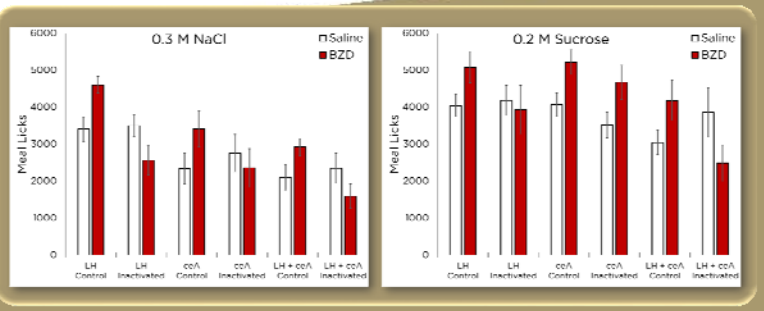
The parabrachial nucleus (PBN) receives input from forebrain sites such as the lateral hypothalamus (LH), central amygdala (ceA), and gustatory cortex among others, as well as input from ascending afferent gut- and gustatory-related signals. Thus, the PBN is an ideal nexus for afferent gustatory signal modulation by ascending and descending signals related to post-ingestive, motivational, and learned cues. Previously we found that PBN application of the benzodiazepine (GABA-A agonist), chlordiazepoxide (CDP), increased licking to appetitive and aversive tastants but it did not affect licking to water or capsaicin, a trigeminal stimulus. We are now using the Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technique to selectively and transiently inactivate specific pathways to the PBN.



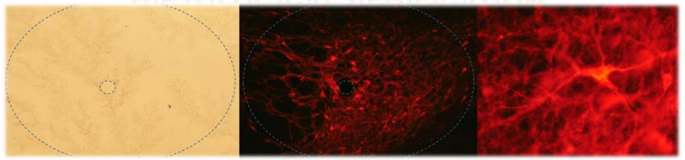


IntraPBN injections (0.3 µL at 0.1 µL / min) Inactivated = CNO (clonzopine-N-oxide, DREADD ligand) & Control = aCSF; Saline & benzodiazepine (BZD = CDP at 10 mg/ml/kg b.w.) administrated via i.p. injection



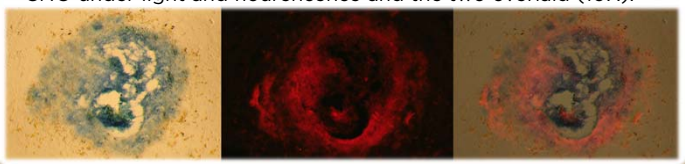
Selective & transient silencing of ceA, LH, and LH+ceA projections within the PBN produced dissociable effects on consumatory behaviors. LH projections appear to be involved in the numbers of bursting cycles within a meal while ceA projections appear to be involved in hedonic evaluation of tastants. Both LH and ceA projections appear to contribute to the motivation to consume salt and sweet tastants. The effect of silencing of ceA, LH, & LH+ceA projections within the PBN were limited to behaviors influenced by the PBN and did not affect oromotor functions (ILIs) influenced by BZDs within other hindbrain nuclei.

HISTOLOGICAL VERIFICATION

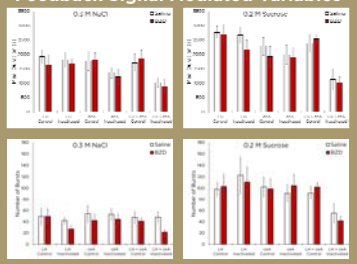


ABOVE: Target site with injection tract (10X) under light and fluorescence; single neuron infected with DREADD (40X).

BELOW: PBN with ink injection at same volume as DREADD ligand CNO under light and flourencence and the two overlaid (10X).

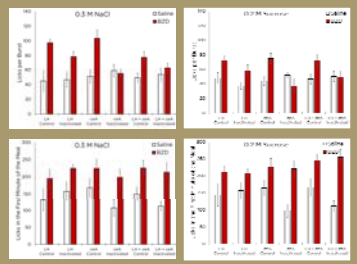


Postingestive / Postabsorpotion Feedback Signal Mediated Variables



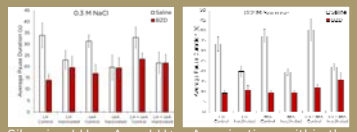
Silencing the ceA projection within the PBN slightly reduced meal duration for salt while silencing LH+ceA projections significantly reduced the meal duration for salt and sweet regardless of saline/BZD condition. Silencing the LH projection reduced the number of burst for salt only under the influence of BZD while silencing LH+ceA projections reduced the number of bursts for sweet in both conditions.

Orosensory Mediated Variables



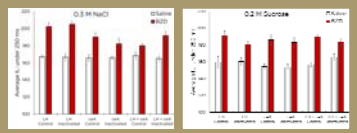
Replicating previous findings, BZD increased licks per burst and licks in the first minute of testing. Silencing the ceA or LH+ceA projections eliminated BZD increased licks per burst for salt and sweet. Silencing of ceA or LH+ceA projections within the PBN reduced first minute licks to salt and sweet but only under saline conditions.

Motivation to Lick



Silencing LH, ceA, or LH+ceA projections within the PBN reduced the pause duration for salt and sweet only under the saline condition.

Oromotor Coordination



ACKNOWLEDGEMENTS

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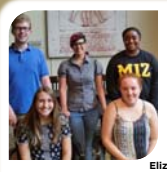

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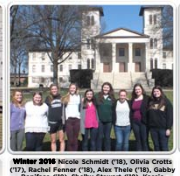

Winter 2016 Nicole Schmidt ('18), Olivia Crotts ('17), Rachel Fenner ('18), Alex Thale ('18), Gabby Boniface ('18), Shelby Stewart ('18), Kassie Franck ('19), Vanessa Zarubin ('18), & Mary Elizabeth Bruner ('19)

From left to right: Nicole Schmidt ('18), Olivia Crotts ('17), Rachel Fenner ('18), Alex Thale ('18), Gabby Boniface ('18), Shelby Stewart ('18), Kassie Franck ('19), Vanessa Zarubin ('18), & Mary Elizabeth Bruner ('19)