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Affilative Social Interactions Activate Vasopressin-Responsive Neurons in the Mouse Dorsal Raphe
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Introduction
Social behavior is inevitably linked to human health shaping both our susceptibility and resilience to diseases and stress. Poorer outcomes are seen in patient populations suffering from stress and improve treatment outcomes, whereas negative interactions such as abuse, social isolation, of bullying can increase aggression and precipitate mood disorders. Discovering the structure and function of neural circuits underlying social behavior is critical to understanding the links between social interaction and health.

The neuropeptide vasopressin has been implicated in the regulation of multiple social interactions including social memory, aggression, mating, pain handling, and parental care. Vasopressin producing neurons in the bed nucleus of the stria terminale (BNST) and medial amygdala (MeA), in particular, are predicted to be involved in social behavior. While the innervation targets of BNST and MeA vasopressin neurons and patterns of vasopressin receptor binding have been well-documented in multiple species, the identity and functional characteristics of neurons targeted by vasopressin innervation is less well understood.

In situ hybridization data suggests that Avpr1a activation in the DR may be stimulus specific. The immediate early gene, c-Fos, is used as a proxy for neural activation. Avpr1A-GFP mouse are found primarily in both BNST and MeA vasopressin neurons and in the dorsal raphe, a target of the BNST vasopressin system.

Who are the vasopressin responsive neurons of the dorsal raphe?

Vasopressin Social Behavior Network

Fos expression in BNST of male mouse exposed to female mouse (Ho et al., 2010)

Fos expression in dorsal raphe of male mouse exposed to female mouse

Overall increase in Fos expression induced by exposure to a female stimulus animal occurs largely in Avpr1a and non-Avpr1a, non-serotonergic neurons.

Action potentials differ between vasopressin-responsive neurons and serotonergic neighbors

Future directions: Use transcriptome analysis to identify genes that underlie Avpr1a-neuron excitability and neurochemical phenotype.

Vasopressin and Tryptophan Hydroxylase

Coronal brain slice through rostral dorsal raphe

Vasopressin and Tryptophan Hydroxylase

In situs hybridization for Avpr1a, tryptophan hydroxylase, and c-fos mRNA (a gene up-regulated by neuronal activity) revealed that, in both male and female subjects, exposure to a female stimulus animal increased c-fos expression in the DR both in Avpr1a+ neurons and non-Avpr1a neurons.

Our data verify the existence of AVP/vasopressin neurons in the DR and suggest that activation of Avpr1a+ neurons in the DR is stimulus specific, and may be initiated by more affiliative, less antagonistic interactions.

Avpr1a+ neurons have distinct physiological properties compared to neighboring serotonin neurons. Avpr1a+ neurons have small amplitude short duration action potentials. During the after-hyperpolarization Avpr1a+ neurons have depolarizing after potential. These properties likely facilitate the high firing rates observed in these neurons.

Preliminary gene expression studies suggest a number of candidate ion channels that may underlie the hyper-excitability profile of dorsal raphe Avpr1a+ neurons.

Further study is needed to fully interrogate the function of Avp pathways, but one function of the BNST/MeA system appears to be activation of the neurons in the DR with potential excitatory influence on serotonin neurons.

Future work will focus on validating expression of specific ion channel genes and seek to identify the functional role of dorsal raphe Avpr1a+ neurons.

References
Ho et al. (2016) Hormones and Behavior, 82C(0): 368-77
Niederkofler et al. (2016) Cell Reports, 17(8):1934-49

Results & Conclusions
Vasopressin neurons in the dorsal raphe are activated by mating stimulus. A subset of neurons in the dorsal raphe, a target region of extended amygdala vasopressin neurons, is also activated by mating as measured by increases in c-fos.

In situ hybridization for Avpr1a, tryptophan hydroxylase, and c-fos mRNA is up-regulated by neuronal activity. The pattern of staining presented in this poster was supported by the NIMH through grants F32 MH096393 and K01 MH109712 awarded to B.D.R. Avpr1a-GFP mice were generated through the GENSAT program and obtained from the Mutant Mouse Resource & Research Center.

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