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Affiliative Social Interactions Activate Vasopressin-Responsive Neurons in the Mouse Dorsal Raphe

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Affiliative Social Interactions Activate Vasopressin-Responsive Neurons in the Mouse Dorsal Raphe

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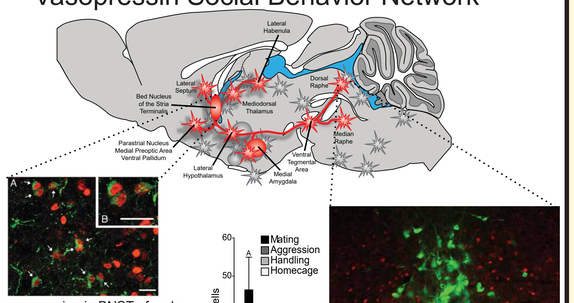
Introduction

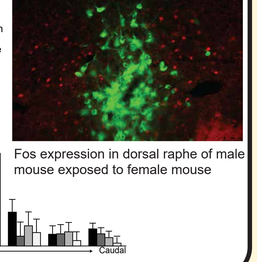
Social behavior is inextricably linked to human health shaping both our susceptibility and resilience to disease and stress. Positive interactions as simple as maternal contact or friendships among children and adults can protect against emotional distress and improve treatment outcomes, whereas negative interactions such as abuse, social isolation, or bullying can increase aggression and precipitate mood disorders. Discovering the structure and function of neural circuits underlying social behavior is critical to understanding the link between social interaction and health.

The neuropeptide vasopressin has been implicated in the regulation of multiple social interactions including social memory, aggression, mating, pair-bonding, and parental care. Vasopressin producing neurons in the bed nucleus of the stria terminalis (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 are less well understood.

Vasopressin Social Behavior Network



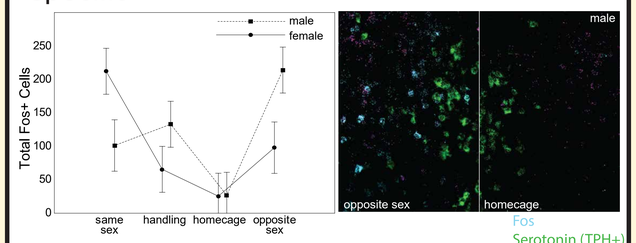
Fos expression in BNST of male mouse exposed to female mouse (Ho et al., 2010)



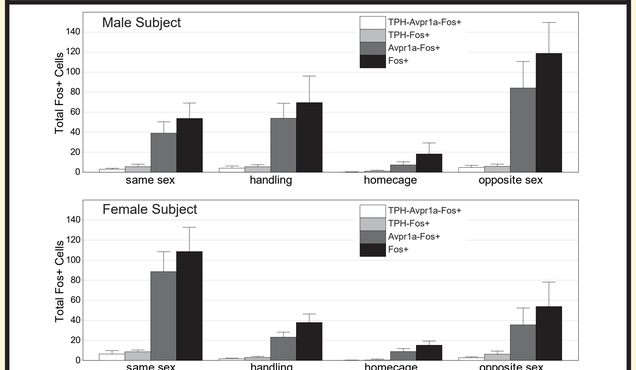
Fos expression in dorsal raphe of male mouse exposed to female mouse

The immediate early gene, c-Fos, used as a proxy for neural activation is expressed in response to a female, but not an unfamiliar male in both BNST vasopressin neurons and in the dorsal raphe, a target of the BNST vasopressin system.

In situ hybridization data suggests that Avpr1a activation in the DR may be stimulus specific

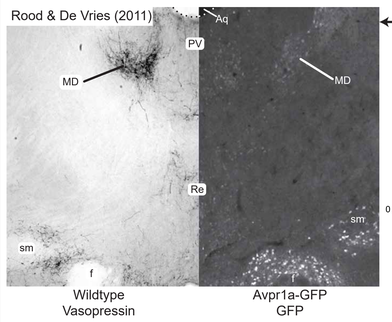


Both female and male subject mice increase fos expression in the Dorsal Raphe when exposed to a female stimulus animal.



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

Avpr1a-GFP mouse: GFP expression mirrors AVP innervation zones and GFP+ neurons respond to vasopressin

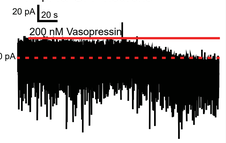


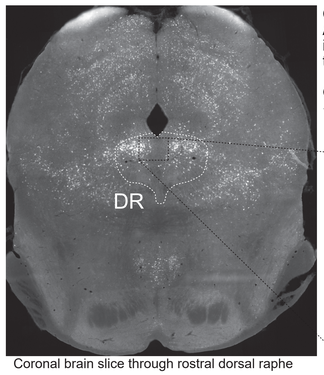
Coronal section through thalamus illustrates mirroring of vasopresisn innervation and Avpr1a-GFP neurons

Wildtype Vasopressin

Avpr1a-GFP GFP

Vasopressin induces inward (excitatory) currents in patched Avpr1a-GFP neurons



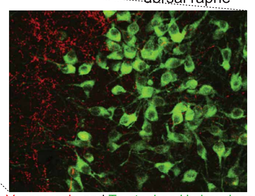


Coronal brain slice through rostral dorsal raphe

Cells expressing GFP in the Avpr1a-GFP mouse are found primarily in location where vasopressin innervation have been previously described.

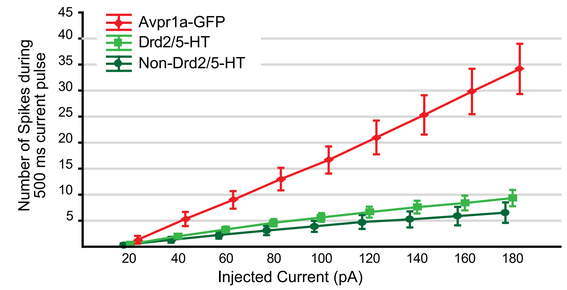
GFP-expressing neurons

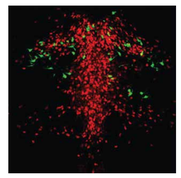
Vasopressin innervation in the dorsal raphe



Vasopressin and Tryptophan Hydroxylase

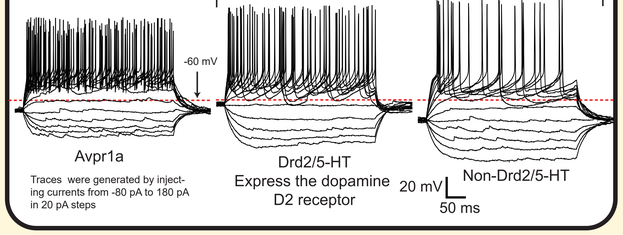
Avpr1a-GFP neurons are highly excitable compared to multiple subtypes of neighboring serotonin neurons





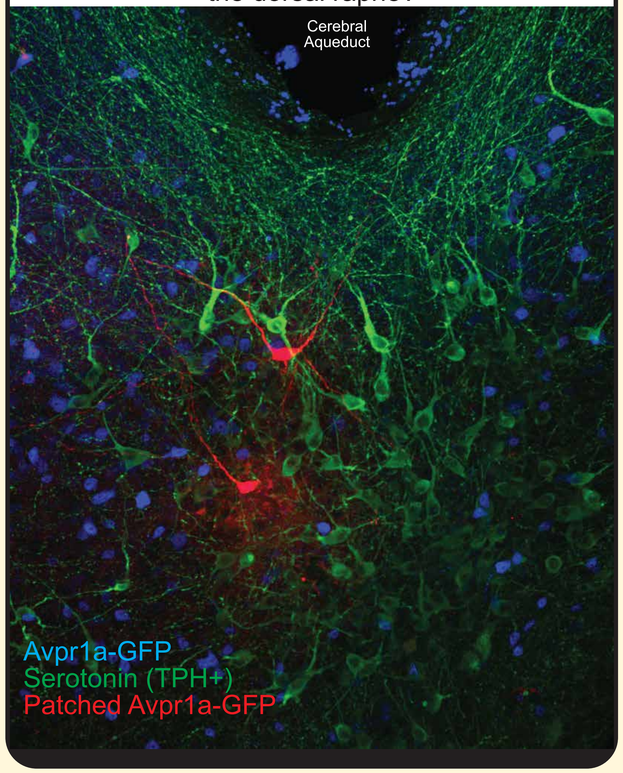
Drd2/5HT and Non-Drd2/5-HT in mid DR

Serotonin neuron subtypes

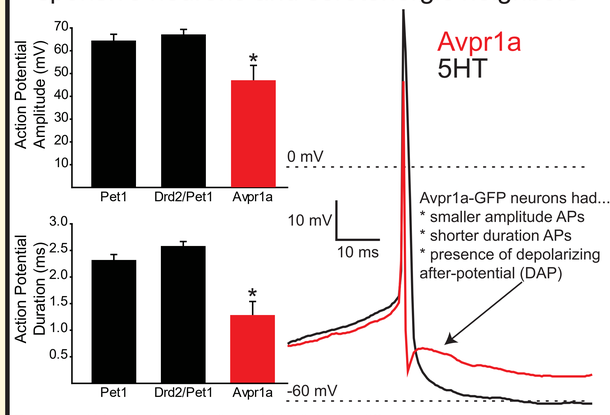


Traces were generated by injecting currents from -80 pA to 180 pA in 20 pA steps

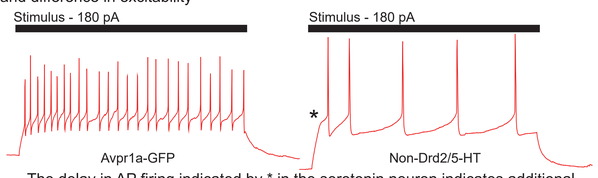
Who are the vasopressin responsive neurons of the dorsal raphe?



Action potentials differ between vasopressin-responsive neurons and serotonergic neighbors

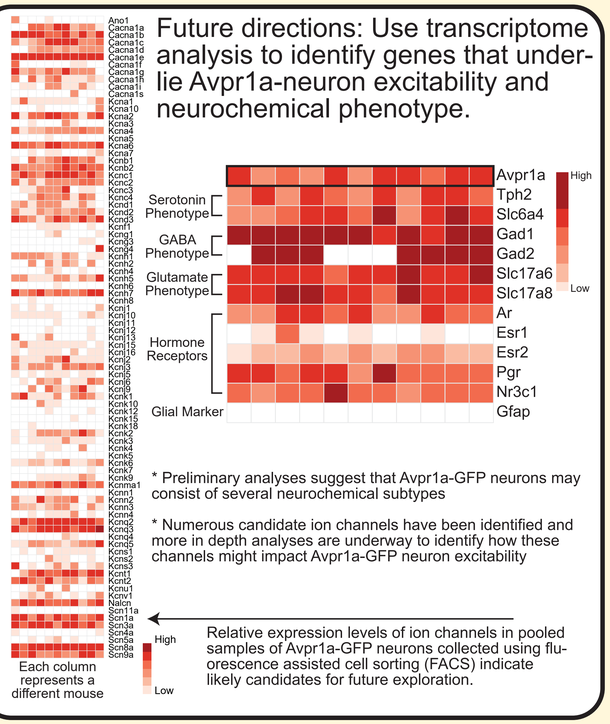


Traces at 180 pA stimulation (below) highlight the differences in action potential shape and difference in excitability



The delay in AP firing indicated by * in the serotonin neuron indicates additional currents may slow firing in the subtype

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



* Preliminary analyses suggest that Avpr1a-GFP neurons may consist of several neurochemical subtypes

* Numerous candidate ion channels have been identified and more in depth analyses are underway to identify how these channels might impact Avpr1a-GFP neuron excitability

Each column represents a different mouse

Relative expression levels of ion channels in pooled samples of Avpr1a-GFP neurons collected using fluorescence assisted cell sorting (FACS) indicate likely candidates for future exploration.

Results & Conclusions

Vasopressin neurons in the extended amygdala are activated by mating stimuli. 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 (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-responsive 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

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First demonstrated interaction between vasopressin and serotonin neurons in the dorsal raphe

Gong et al. (2003) Nature, 425(6961):917-25
GENSAT mouse program

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