The aversive quality of thirst drives the desire to quench it.





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NEUROSCIENCE

# *Neurons that drive and quench thirst*

## Median preoptic neurons modulate water intake and the urge to drink

*By* **Claire Gizowski** *and* **Charles W. Bourque**

Thirst is a vital primordial emotion that motivates fluid intake to compensate for incessant water loss incurred as a result of breathing, sweating, and urine production. Indeed, the maintenance of adequate hydration is a prerequisite for life and, accordingly, the desire to drink emerges as soon as the body's water content declines by 1 to 2%, and this feeling intensifies progressively with further depletion (*1*–*3*). Although regions in the brain that are critical for water intake have been known for more than 60 years, the identification and functional analysis of thirst-related neurons only became possible with the recent advent of genetically targeted photoactivation and photometry, methods that respectively allow manipulation and monitoring of electrical activity in vivo, using fiber-optic microprobes (*4*–*7*). On page 1149 of this issue, Allen *et al.* (*8*) reveal the existence of neurons that specifically encode the intensity and aversive quality of thirst within the median preoptic nucleus (MnPO) of the hypothalamus.

Previous studies have identified primary sensory neurons and pathways that can drive homeostatic forms of thirst, as well as water intake that occurs in anticipation of an impending deficit (*1*). For example, decreases in blood volume (hypovolemia) can promote homeostatic thirst through the activation of cardiopulmonary receptors that relay signals to forebrain thirst regions via poorly understood mechanisms involving the regions of the brain called the nucleus tractus solitarius (NTS) and parabrachial nucleus (PBN) (*3*), and by activation of subfornical organ (SFO) neurons in response to increased concentrations of circulating angiotensin II (*2*, *9*). Similarly, increases in the electrical activity of intrinsically osmosensitive neurons in the organum vasculosum lamina terminalis (OVLT) can drive homeostatic water intake in response to systemic hypertonicity (which occurs when the amount of water decreases) (*1*). Excitation of these neurons by an input from the suprachiasmatic nucleus, the internal "body clock," induces anticipatory water intake prior to sleep (*10*). Although functional imaging studies in humans have indicated that perception of thirst may involve the anterior cingulate cortex (ACC) and in-

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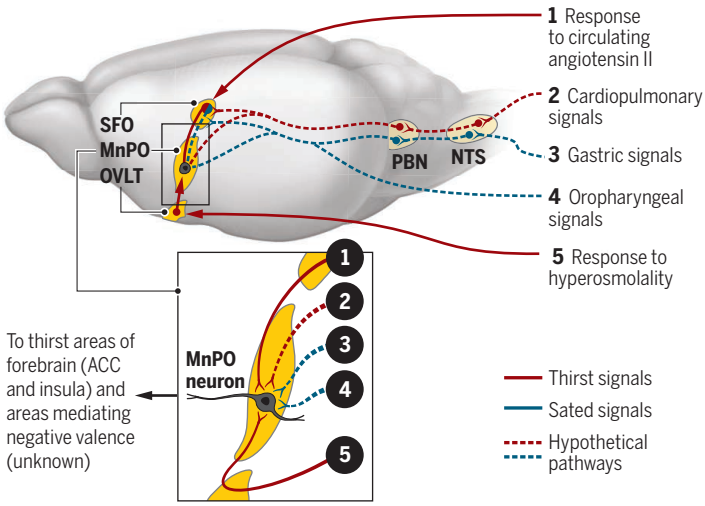
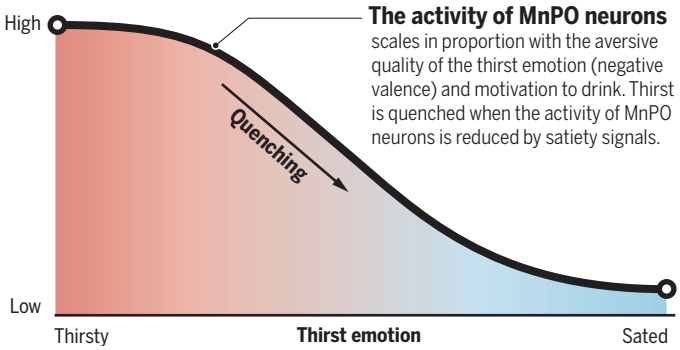
sula (*11*), it remained unknown if the multiple stimuli that can drive thirst can be integrated at the subcortical level and whether such neurons could also encode qualities of the emotion that serve to motivate water-intake behavior, such as negative valence (the aversive feeling evoked concurrently with thirst).

Using transgenic mice in which gene expression can be directed to specific subsets of physiologically activated cells, Allen *et al.* identified a subset of glutamatergic MnPO neurons, the activity of which varies in proportion to the intensity of the drive for water intake invoked by dehydration, a stimulus that causes both hyperosmolality and hypovolemia. The MnPO is interposed between the SFO and OVLT, and neurons in this area receive information from brainstem nuclei including the NTS and PBN. Notably, the authors found that glutamatergic MnPO neurons could be activated by hypertonicity alone, suggesting that they receive osmosensory signals from the OVLT. Moreover, retrograde tracing with a virally mediated labeling approach showed that these specific neurons also receive synaptic inputs from the SFO and PBN. Therefore, MnPO neurons are well poised to integrate multiple thirst-generating stimuli (see the figure).

## Thirst-encoding neurons

The MnPO of the hypothalamus contains neurons that integrate multiple thirst-generating stimuli (1 to 5).




**The activity of MnPO neurons** scales in proportion with the aversive quality of the thirst emotion (negative valence) and motivation to drink. Thirst is quenched when the activity of MnPO neurons is reduced by satiety signals.

According to the "drive reduction" hypothesis of goal-directed behavior, dehydration should promote water intake to suppress the negative valence of the thirst emotion. If and how this can be achieved at the neuronal level was unknown before now. Using fiber photometry to monitor GCaMP fluorescence changes as a surrogate for population firing, the authors found that MnPO neuron activity is proportionally scaled to the intensity of the aversive state. As mice ingested water to quench thirst, fluorescence intensity decreased; conversely, fluorescence intensity increased in response to thirst-promoting stimuli, such as hypertonicity. Moreover, using water-replete mice trained to press a lever to obtain water, the authors showed that photoactivation of MnPO neurons at different frequencies causes a proportional increase in lever pressing. Thus, the activity of MnPO neurons is proportional to thirst and is sufficient to drive water intake. Next, evidence that MnPO neurons can encode negative valence associated with thirst was provided by two observations: A real-time place preference assay revealed that mice avoid the side of the chamber associated with photoactivation of MnPO neurons, indicating that MnPO neuron activity is aversive; and, mice provided with an opportunity to shut off photoactivation of MnPO neurons by lever pressing did so vigorously. Thus, MnPO neuron activity proportionally encodes the aversive sensation of thirst and drives water intake to reduce activation of these neurons.

Similar to findings in the SFO (*9*), Allen *et al.* observed that suppression of MnPO neuron activity and cessation of water intake in thirsty mice that were provided water ad libitum occurred well before osmolality and volemia could be restored through gastric reabsorption. Moreover, when water repletion was slowed through lever-pressing protocols, neuronal activity declined gradually until a minimum level was reached that coincided with the cessation of drinking. These data indicate that the MnPO neurons receive quantitative real-time feedback information from afferent inputs that proportionately inhibit MnPO neuron activity as satiety is progressively achieved through water intake.

Therefore, the suppression of MnPO neuron activity during water intake must be mediated by satiety signals ascending directly or indirectly from interoceptive gastric inputs (*12*) or oropharyngeal inputs (*9*, *13*). Indeed, solute and stretch receptors send signals to brainstem nuclei such as the PBN and NTS (*14*, *15*), which may then provide regulatory inputs to the MnPO to inhibit neuron activity. Additionally, oropharyngeal signals can inhibit SFO neurons that drive water intake (*9*), suggesting that signals of this type could contribute to the early inhibition of MnPO neurons either directly or via the SFO.

The study of Allen *et al.* has made substantial strides toward illuminating how a subset of MnPO neurons mediates water intake and encodes emotional qualities associated with thirst. However, several avenues remain to be explored. For example, it is unclear how the activity of MnPO neurons stimulates thirst, and whether this involves a projection to cortical regions such as the ACC and insula. Also unclear is how negative-valence information encoded by MnPO neurons is relayed to central sites that confer the aversive qualities of thirst, whether there is a role for reward signals (positive valence), and how satiety signals are relayed to the MnPO. Future studies aimed at answering these questions will enhance our understanding of this essential primordial emotion. ■

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