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# Neural populations for maintaining body fluid balance

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## Abstract

Fine balance between loss-of water and gain-of water is essential for maintaining body fluid homeostasis. The development of neural manipulation and mapping tools has opened up new avenues to dissect the neural circuits underlying body fluid regulation. Recent studies have identified several nodes in the brain that positively and negatively regulate thirst. The next step forward would be to elucidate how neural populations interact with each other to control drinking behavior.

## Introduction

Thirst is an instinctive drive that prompts animals toward intense water seeking and consumption to restore body fluid balance. Precise tuning of fluid balance is essential for survival. Classical and contemporary studies across species have unveiled the basic principles of thirst regulation.

In this review, we will briefly overview fluid regulatory mechanisms conserved in many species, and summarize gain-of-function and loss-of-function studies of neural populations and circuitry. Second, we will describe our current understanding of the mechanisms involved in thirst quenching and satiety.

## Driving of thirst

### Thirst driving system across species and gain of function studies

In many species, Angiotensin II (Ang II) along with systemic osmolality plays important roles in driving thirst and drinking behavior. The dipsogenic effect of Ang II was first demonstrated in rodents: intracranial injection of Ang II into the third ventricle and other brain areas immediately induced water drinking behavior [1]. Besides rodents, rhesus monkeys [2–4], goats [5,6], cows [7], sheep [8], pigs [9,10], dogs [11,12], and cats [13–15] have been found to drink water in response to intracranial administration of Ang II. These studies were followed up by electrical stimulation of the lamina terminalis (LT), a major site of Ang II action that increases fluid intake in several mammalian species (Table 1). Ang II also causes water drinking behavior in reptiles, amphibians and birds [1,16]. Interestingly,

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studies in aquatic amphibious fishes revealed a unique system of Ang II-related thirst regulation. In mudskipper, Ang II stimulates the area postrema (AP), a hindbrain nucleus, to induce swallowing action [17,18]. Recent studies with contemporary neural manipulation tools have expanded our knowledge of thirst circuits at a finer resolution. In particular, optogenetic manipulation using light-sensitive channels [19], and Designer Receptors Exclusively Activated by Designer Drugs (DREADD)-based chemogenetic manipulation [20] allowed to link the activity of a specific neural population with behavioral outcome. The LT is composed of three structures; the subfornical organ (SFO), the organum vasculosum of the lamina terminalis (OVLT) and the median preoptic nucleus (MnPO). Of these, SFO and OVLT lack the normal blood–brain barrier, and have direct access to circulation. Recently, several genetically defined neural populations related to thirst have been identified in the LT [21,22] (Table 1). Stimulation of a glutamatergic population of SFO neurons marked by the expression of the transcription factor ETV-1 [23••], nitric oxide synthase 1 (nNOS) [23••,24••,25] and $Ca^{2+}$/calmodulin-dependent kinase II (CamKII) [23••, 26], evoked voracious drinking of water. The MnPO also has excitatory populations expressing nNOS or adenylate cyclase activating polypeptide 1 (Adcyap1) that positively regulate drinking behavior [27••,28]. Similarly, in the OVLT, nNOS – or angiotensin 1A receptor (Agtr1a) – expressing neurons were identified as thirst-promoting neurons [27••, 28].

Outside the LT, vasopressin-expressing neurons in the suprachiasmatic nucleus (SCN) that project to thirst neurons in the OVLT have been shown to mediate anticipatory thirst before sleep [29•]. The lateral hypothalamic area (LHA) is also known for regulating ingestive behavior [30]. A recent study reported that activation of neurotensin (Nts)-expressing LHA neurons promotes fluid but not food intake [31]. Because LHA is one of the major downstream target of thirst neurons in the MnPO [27••,28,32•], it is possible that Nts neurons may receive direct inputs from the LT to relay thirst information to the next brain station.

We note that the LT is also implicated in the regulation of sodium ingestion. A study showed that SFO neurons expressing Agtr1a mediate sodium intake [33]. It is intriguing that $SFO^{Agtr1a}$ neurons seem to be a subset of $SFO^{nNOS}$ neurons, but their activation drives sodium intake instead of water. Future studies are required to reconcile how appetites for water and sodium are encoded by partially overlapping SFO excitatory neurons.

## Loss-of-function studies of the LT

In parallel to gain-of-function studies, several loss-of-function techniques have been employed in the past few decades to study the functional necessity of a given neural circuit (Table 2). Early studies demonstrated that radio-frequency lesions of forebrain areas including the LT disrupted fluid balance and thirst mechanisms in goats [34] and rats [35,36]. The physical destruction of the neural connection between the SFO and MnPO has been shown to attenuate water intake in rats [37,38]. Consistently, in rats with lesions of the SFO and OVLT, there was a decrease in the number of Fos-like immuno-reactive neurons in the MnPO, following intravenous infusion of hypertonic saline solution [39]. Moreover, ablation of the MnPO by multiple techniques such as electrolytic ablation [40] or ibotenic

acid [41] all blocked drinking behavior. A comprehensive study in sheep also supports this view: radiofrequency ablation of MnPO reduced drinking behavior, but ablation of the OVLT or SFO alone had minor effects on drinking in response to hypertonic saline [42]. Taken together, ablation of individual nuclei of the LT (with the most profound effects by MnPO ablation) has an impact on angiotensin-induced or hypertonicity-induced drinking.

Classical loss-of-function approaches generally affect all neurons in a given brain area, whereas recent manipulation tools can be used to silence/ablate a genetically defined neural population. Augustine *et al.* applied cell-type-specific ablation by caspase [43] to individual nuclei of the LT. The study revealed that $MnPO^{nNOS}$ neurons are essential for driving drinking behavior induced by photostimulation of $SFO^{nNOS}$ neurons [27••]. By contrast, stimulation of $MnPO^{nNOS}$ neurons after ablating $SFO^{nNOS}$/$OVLT^{nNOS}$ still triggered drinking. Thus, the $MnPO^{nNOS}$ neuronal population is required to integrate the signals from thirst-driving neurons of the SFO [27••]. However, there are some discrepancies regarding the requirement of SFO neurons for drinking. Permanent ablation of the SFO [42,44,45] or $SFO^{nNOS}$ neurons (unpublished) had temporally/minimum effect on water intake. In contrast, acute optogenetic inhibition of $SFO^{nNOS}$ neurons [24••], or the SFO → OVLT projection [33] using archaerhodopsin significantly attenuated water intake. Although precise mechanisms are unknown, it is feasible that the function of $SFO^{nNOS}$ neurons may be required for drinking in short periods, but permanent ablation induces neural plasticity over time that compensates for the loss of SFO neurons to maintain body fluid balance.

## Quenching of thirst

### Functional studies of the LT

Thirsty animals including humans stop drinking water before the systemic environment recovers (rehydration). This early termination of drinking was known both behaviorally and endocrinologically. For instance, studies in dogs [46,47] and rhesus monkeys [48] with a gastric fistula showed that only sham-drinking rapidly inhibited vasopressin release from the brain. On the basis of these observations, it was proposed that there may be thirst-quenching neural circuits that respond to drinking. More recently, drinking water has been shown to inhibit the activity of thirst-related neurons [24••,27••,32••,49•]. These studies suggested that water intake stimulates thirst-quenching signals in the brain that leads to rapid drinking termination.

At the circuit level, we have just begun to get handles on thirst-quenching neurons mainly in the LT. It was demonstrated that the activation of GABAergic neurons in the SFO ($SFO^{VGAT}$) suppresses water intake in thirsty animals [23••]. Similarly, optogenetic activation of inhibitory neurons in the MnPO/OVLT suppressed water intake [27••,50•]. Thus, it appears that stimulation of inhibitory populations in the LT quenches thirst in general.

Although LT inhibitory neurons are sufficient to inhibit drinking, few studies have addressed their physiological role related to thirst quenching. Our laboratory tackled this question by optical recording from individual neural populations in the LT. We showed that MnPO inhibitory neurons that coexpress glucagon-like peptide 1 receptor ($MnPO^{GLP1R}$) are

activated upon gulping action regardless of liquid type, and they send mono-synaptic inhibition to $SFO^{nNOS}$ neurons [27••]. These experiments implicated that $MnPO^{GLP1R}$ neurons receive signals from the oropharyngeal areas in response to drinking. Sensory stimuli from the oropharyngeal area are generally transported through cranial nerves V, VII, IX, and X to the central pattern generator within the nucleus tractus solitarius (NTS), which elicits swallowing action. Although fluid-sensing mechanisms in the peripheral area remain poorly understood, $MnPO^{GLP1R}$ neurons may receive oropharyngeal inputs from other brain regions such as the NTS, and provide rapid quenching of thirst circuits.

### Functional studies of other brain regions

Several other brain regions are also implicated in thirst-quenching. The NTS receives peripheral inputs including visceral and baroreceptor signals [51–54], and is known to regulate various appetites [53,55,56]. For example, optogenetic stimulation of cholecystokinin (CCK) expressing NTS neurons decreases feeding [57]. Lesions of NTS neurons have been reported to cause overdrinking in rats [51,52] suggesting that the NTS plays a role in optimizing water intake. However, distinct neural populations that control water intake remain unknown. Another hindbrain structure related to thirst-quenching is the parabrachial nucleus (PBN). Stimulation of oxytocin receptor-expressing neurons in the PBN ($Oxtr^{PBN}$ neurons) has been shown to suppress fluid intake, but not food or salt intake [58•]. The PBN is one of the major projection sites of NTS neurons [59] that forms reciprocal connections with forebrain areas [60–63]. It is possible that the PBN relays thirst-quenching signals from the NTS to forebrain regions such as the MnPO.

Although recent studies have pinpointed multiple thirst-quenching nodes, it is still unclear how activation of these neurons suppresses drinking. Do they reduce the valence of water, or the motivation to drink? Currently, understanding of emotional and conscious processing of thirst is severely limited. On the basis of anatomical connections in rodents [64] and functional studies in humans [65], the LT-thalamus-insular/cingulate cortex axis may be related to the genesis of thirst perception.

## Conclusions and future directions

1. Efferent connections from the LT to other brain regions for driving thirst.

   The brain regions including the LT, NTS, PBN, and insular/cingulate cortex have been all implicated in fluid regulation. However, how interoceptive information from the LT is processed in downstream neural circuits remains unknown. Future studies should focus on identifying the specific circuitry from the LT and functionally annotate individual neural populations to behavioral and hormonal outputs related to thirst.

2. How do peripheral organs sense drinking and send signals to thirst-quenching neurons?

   Water intake stimulates multiple sensory signals including taste [66], oropharyngeal gulping motion, and osmolality changes in the gut (Figure 1) [67]. Interestingly, one thirst-quenching population (e.g. $MnPO^{GLP1R}$ neurons)

represents a specific aspect of drinking behavior (in this case, liquid gulping). However, there are still important questions remain to be answered. Are there distinct types of thirst-quenching neurons that detect other sensory stimuli evoked by water intake? How does each neural population 'know' that peripheral drinking events have occurred? Recent development of *in vivo* optical recording, manipulation, and tracing tools will help identify molecular and neural basis of thirst-quenching and satiety.

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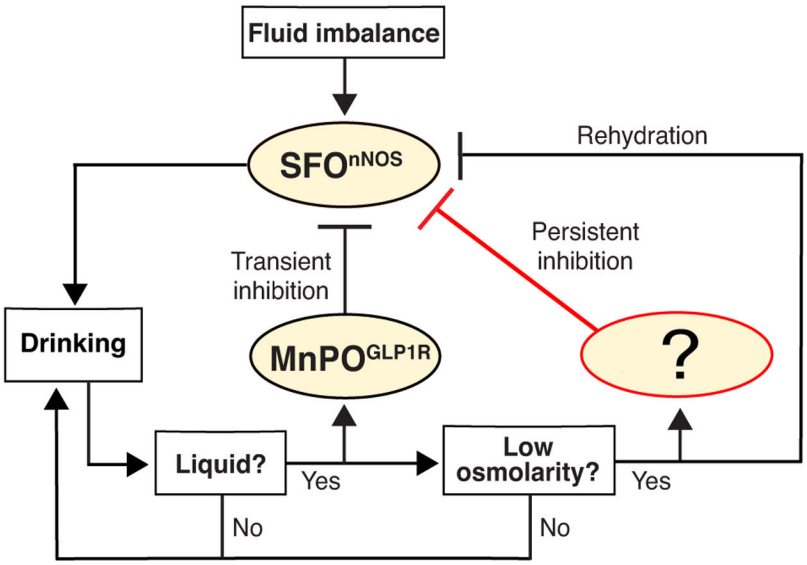


**Figure 1.**

Flow chart of the inhibitory effects on the SFO thirst driving neurons. After ingestion, the $MnPO^{GLP1r}$ neurons quickly respond to drinking of any types of liquid, and provide transient inhibition to the $SFO^{nNOS}$ neurons. It remains unknown which neurons are specifically activated by hypo-osmolarity induced by water ingestion and send the persistent inhibitory signal to the SFO.

**Table 1**

Gain of function studies related with the LT

| Brain part or cell types | Method of manipulation | Phenotype | Species | Ref. |
|---|---|---|---|---|
| SFO | Ang II injection | Water intake ↑ | Rat | [68,69] |
| | | | Japanese quail | [70] |
| | Electrical stimulation | Water intake ↑ | Rat | [71,72] |
| | | AVP secretion ↑ | Rat | [73] |
| POA | Ang II injection | Water intake ↑ | Cat | [14] |
| | | Water intake ↑; AVP secretion ↑ | Rhesus monkey | [3,4] |
| | | Water intake ↑ | Japanese quail | [74] |
| SFO, POA | Ang II injection | Water intake ↑ | Dog | [11] |
| MnPO | Ang II injection | Water intake ↑ | Rat | [75] |
| $SFO^{nNOS}$, $sFO^{camkII}$, $SFO^{ETV1}$ | ChR2 | Time-locked water intake upon photostimulation | Mouse | [23••,24••,25,27••] |
| $SFO^{nNOS}$, $SFO^{camkII}$ | Gq-DREADDs | Water intake ↑ | Mouse | [25,26,27••] |
| $MnPO/OVLT^{GLUT}$ | ChR2 | Water intake ↑ | Mouse | [50•] |
| $_{MnPO}{}^{nNOS}$ | ChR2 | Time-locked water intake upon photostimulation | Mouse | [27••] |
| $MnPO^{Adcyap1}$ | ChR2 | Water but not NaCl intake | Mouse | [28] |
| $_{OVLT}{}^{nNOS}$ | ChR2 | Time-locked water intake upon photostimulation | Mouse | [27••] |
| $OVLT^{Agtr1a}$ | ChR2 | Water but not NaCl intake | Mouse | [28] |
| $SFO^{GLUT}$ neurons projecting to the MnPO | ChR2 | Time-locked water intake upon photostimulation | Mouse | [24••] |
| $SFO^{GLUT}$ neurons projecting to the OVLT | ChR2 | Time-locked water intake upon photostimulation | Mouse | [33] |
| $SCN^{avp}$ neurons projecting to the OVLT | ChR2 | Time-locked water intake upon photostimulation | Mouse | [29•] |
| $SFO^{GABA}$ | ChR2 | Water intake ↓ (dehydration) | Mouse | [23••] |
| $MnPO/OVLT^{GABA}$ | ChR2 | Water intake ↓ (dehydration) | Mouse | [50•] |
| $MnPO^{GLP1R}$ | ChR2 | Water intake ↓ (dehydration) | Mouse | [27••] |

Adcyap1, adenylate cyclase activating polypeptide 1; Agtr1a, angiotensin 1A receptor; Ang II, Angiotensin II; AVP, arginine vasopressin; AVP secretion ↑; induction of AVP secretion; Camk2, calcium/calmodulin-dependent protein kinase type 2; ChR2, channelrhodopsin2; DREADDs, designer receptors exclusively activated by designer drugs; Etv1, ETS translocation variant 1; GABA, GABAergic; GLUT, glutamatergic; MnPO, median preoptic nucleus; nNOS, neuronal nitric oxide synthase; OVLT, organum vasculosum of the lamina terminalis; POA, preoptic area; SCN, suprachiasmatic nucleus; SFO, subfornical organ; Water intake ↑; induction of water intake; Water intake ↓, reduction of water intake; (dehydration), under water-restricted condition.

**Table 2**

Loss of function studies related with the LT

| Brain part or cell types | Method of lesions or inhibition | Phenotype | AVP secretion | Species | Ref. |
|---|---|---|---|---|---|
| AV3V | Radio-frequency lesions | Adipsia | ↓ | Goat | [34] |
| | | | ↓ [76] | Rat | [35,36] |
| Fibers between the SFO and MnPO | Physical cut | Water intake ↓ (Ang II)<br>Normal ad-lib drinking | – | Rat | [37,38] |
| SFO | Electrolytic lesions | Water intake ↓ (Ang II) | ↓ [77] | Rat | [44] |
| | | Recovered after 2 weeks | | | |
| | | Water intake ↓ (Ang II) | – | Dog | [80] |
| | Radio-frequency lesions | No effect (high NaCl) | ↓ [78] | Sheep | [42,45] |
| MnPO | Electrolytic lesions | Water intake ↓ (Ang II and high NaCl) | ↓ [79] | Rat | [81] |
| | Ibotenate lesions | Water intake ↓ (Ang II and high NaCl) | – | Rat | [41] |
| | Radio-frequency lesions | Water intake ↓ (high NaCl) | ↓ [78] | Sheep | [42,45] |
| OVLT | Electrolytic lesions | Water intake ↓ (high NaCl) | ↓ | Dog | [82] |
| | | No effect (high NaCl) | – | Rat | [83] |
| | Radio-frequency lesions | No effect (high NaCl) | ↓ [78] | Sheep | [42,45] |
| SFO and MnPO | Radio-frequency lesions | Water intake ↓ (high NaCl) | – | Sheep | [42,45] |
| SFO and OVLT | Radio-frequency lesions | Water intake ↓ (high NaCl) | ↓ [78] | Sheep | [42,45] |
| SFO and AV3V | Electrolytic lesions | C-fos in MnPO ↓ (high NaCl) | – | Rat | [39] |
| SFO,MnPO and OVLT | Radio-frequency lesions | Abolished water intake (high NaCl) | ↓ [78] | Sheep | [42,45,84] |
| MnPO and OVLT | Radio-frequency lesions | Abolished water intake (high NaCl) | – | Sheep | [42,45] |
| $SFO^{nNOS}$ | Arch | Abolished water intake (dehydration) | – | Mouse | [24••] |
| SFO neurons projecting to the OVLT | Arch | Water intake ↓ (dehydration) | – | Mouse | [33] |
| $MnPO^{nNOS}$ | Caspase ablation | Water intake ↓ ($SFO^{nNOS}$ or $OVLT^{nNOS}$ stimulation) | – | Mouse | [27••] |
| $MnPO^{GLP1R}$ | Caspase ablation | Liquid intake (saline) ↑ | – | Mouse | [27••] |
| $MnPO^{nNOS}$ | Gi-DREADDs | Abolished water intake (dehydration or $SFO^{nNOS}$ stimulation water) | – | Mouse | [27••] |
| $MnPO^{GLP1R}$ | Gi-DREADDs | Liquid intake (saline) ↑ | – | Mouse | [27••] |
| $SCN^{AVP}$ neurons projecting to the OVLT | Arch | Abolished water intake (before sleep) | – | Mouse | [29•] |

Arch, archaerhodopsin; AV3V, periventricular tissue surrounding the anteroventral third ventricle; AVP, arginine vasopressin; DREADDs, designer receptors exclusively activated by designer drugs; GLP1R, glucagon-like peptide 1 receptor); MnPO, median preoptic nucleus; nNOS, neuronal nitric oxide synthase; N.I., not indicated; OVLT, organum vasculosum of the lamina terminalis; SCN,

suprachiasmatic nucleus; SFO, subformical organ; Water intake ↓, around 50–95% of reduction of water intake; Abolished water intake, around 95–100% of reduction of water intake; (Ang II), response to Ang II administration; (high NaCl), response to hypertonic NaCl administration; (dehydration), under water-restricted condition.