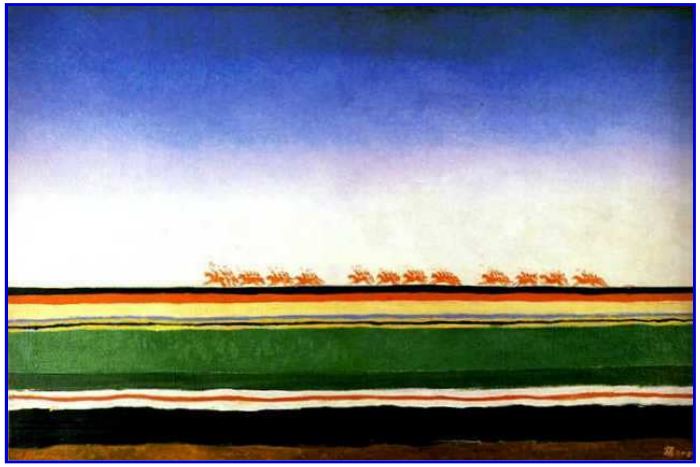
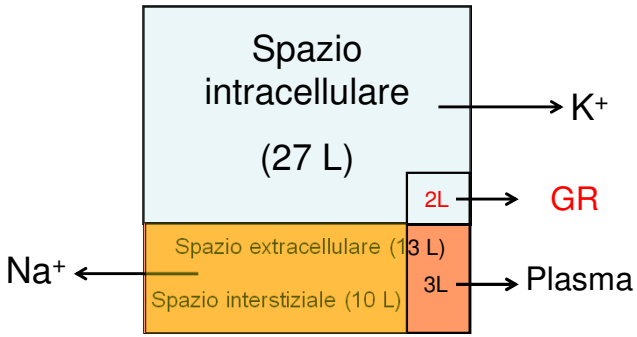
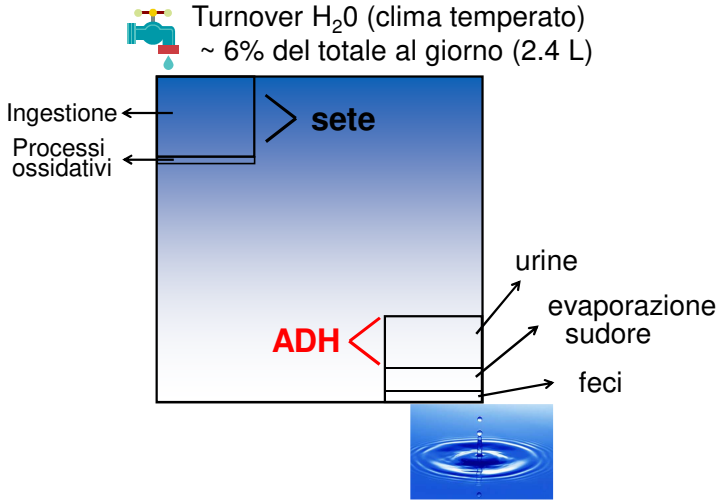
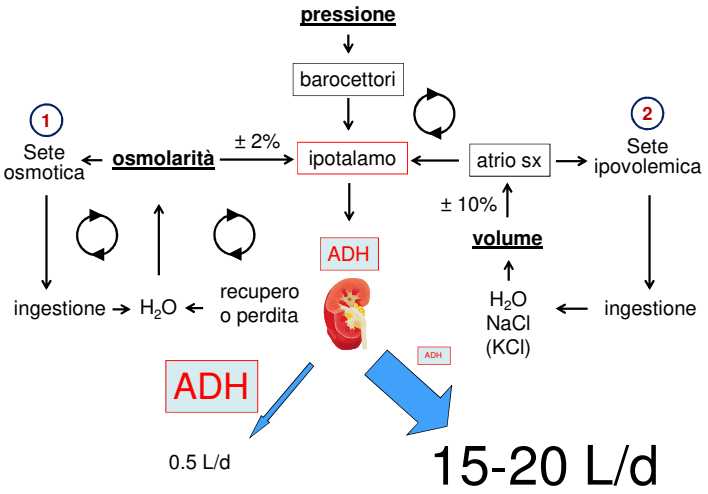


Kazimir Malevich (1879-1935)

H_20 totale ~ 40 L (per 70 kg)







Article

The cellular basis of distinct thirst modalities

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Allan-Hermann Pool[1], Tongtong Wang[1,2], David A. Stafford[3], Rebecca K. Chance[3], Sangjun Lee[1], John Ngai[3,4] & Yuki Oka[1]✉

Fluid intake is an essential innate behaviour that is mainly caused by two distinct types of thirst[1–3]. Increased blood osmolality induces osmotic thirst that drives animals to consume pure water. Conversely, the loss of body fluid induces hypovolaemic thirst, in which animals seek both water and minerals (salts) to recover blood volume. Circumventricular organs in the lamina terminalis are critical sites for sensing both types of thirst-inducing stimulus[4–6]. However, how different thirst modalities are encoded in the brain remains unknown. Here we employed stimulus-to-cell-type mapping using single-cell RNA sequencing to identify the cellular substrates that underlie distinct types of thirst. These studies revealed diverse types of excitatory and inhibitory neuron in each circumventricular organ structure. We show that unique combinations of these neuron types are activated under osmotic and hypovolaemic stresses. These results elucidate the cellular logic that underlies distinct thirst modalities. Furthermore, optogenetic gain of function in thirst-modality-specific cell types recapitulated water-specific and non-specific fluid appetite caused by the two distinct dipsogenic stimuli. Together, these results show that thirst is a multimodal physiological state, and that different thirst states are mediated by specific neuron types in the mammalian brain.

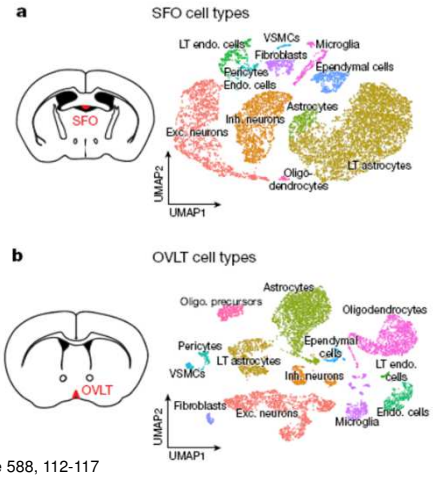
Due tipi di sete: sete iperosmotica e sete ipovolemica

Peripheral sensory systems such as taste and olfaction can detect multiple stimuli through unique cell types. Similarly, the brain can detect at least two distinct thirst-inducing stimuli: an increase in osmolality and a decrease in volume in the systemic circulation. Moreover, these two thirst types, osmotic and hypovolaemic thirst, drive different fluid intake patterns[1]. When the brain detects osmolality elevation, animals only consume water to alleviate hyperosmotic stress. Conversely, reduced systemic volume induces vigorous intake of both water and salts to recover blood volume at the appropriate osmolality. Natural dehydration is a combination of these two stimuli. Therefore, while both types of thirst trigger drinking behaviour, solute preference is drastically different to achieve distinct internal consequences.

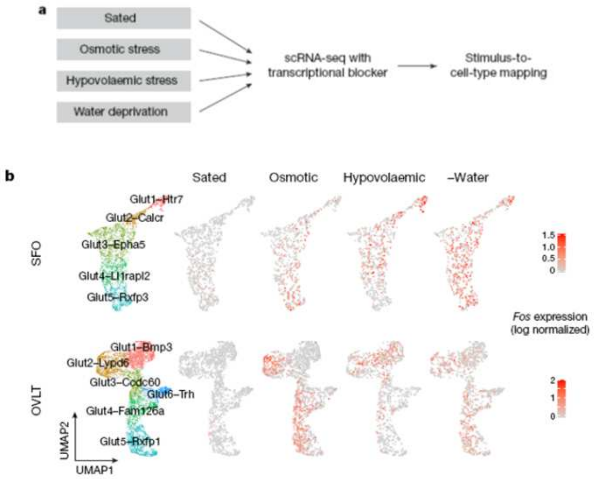
Lamina terminalis circumventricular organs – sensori del bilancio idrosalino

Subfornical organ

Organum vasculosum lamina terminalis



Pool et al. (2020) Nature 588, 112-117



Pool et al. (2020) Nature 588, 112-117

Due organi in parallelo, ridondanza solo parziale?

In mammals, the brain has two osmosensory organs, the SFO and the OVLT, which are functionally redundant for sensing internal water balance. Our transcriptomic analyses enabled a systematic comparison between these two structures at both molecular and cellular levels. Two CVOs largely share corresponding major cell classes and neuron types, and gene expression patterns related to potential osmoregulatory molecules[29] (Extended Data Fig. 3). These results suggest that the SFO and the OVLT are parallel entry points that independently sense fluid balance and drive dedicated downstream behaviours. However, we found that astrocytes in the SFO, but not in the OVLT, are strongly activated by osmotic stress (Extended Data Fig. 4d). Thus, astrocytes in the SFO may have a dedicated function in fluid regulation[30].

Ma …. Il senso di sazietà per l'acqua viene percepito prima che ci sia stata l'equilibrazione osmotica. Quali sono i meccanismi?

Sensory representation and detection mechanisms of gut osmolality change

Il ruolo dell'area portale epatica (HPA)

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Takako Ichiki[1], Tongtong Wang[1], Ann Kennedy[1,2], Allan-Hermann Pool[1], Haruka Ebisu[1], David J. Anderson[1,3] & Yuki Oka[1]✉

Ingested food and water stimulate sensory systems in the oropharyngeal and gastrointestinal areas before absorption[1,2]. These sensory signals modulate brain appetite circuits in a feed-forward manner[3–5]. Emerging evidence suggests that osmolality sensing in the gut rapidly inhibits thirst neurons upon water intake. Nevertheless, it remains unclear how peripheral sensory neurons detect visceral osmolality changes, and how they modulate thirst. Here we use optical and electrical recording combined with genetic approaches to visualize osmolality responses from sensory ganglion neurons. Gut hypotonic stimuli activate a dedicated vagal population distinct from mechanical-, hypertonic- or nutrient-sensitive neurons. We demonstrate that hypotonic responses are mediated by vagal afferents innervating the hepatic portal area (HPA), through which most water and nutrients are absorbed. Eliminating sensory inputs from this area selectively abolished hypotonic but not mechanical responses in vagal neurons. Recording from forebrain thirst neurons and behavioural analyses show that HPA-derived osmolality signals are required for feed-forward thirst satiation and drinking termination. Notably, HPA-innervating vagal afferents do not sense osmolality itself. Instead, these responses are mediated partly by vasoactive intestinal peptide secreted after water ingestion. Together, our results reveal visceral hypoosmolality as an important vagal sensory modality, and that intestinal osmolality change is translated into hormonal signals to regulate thirst circuit activity through the HPA pathway.

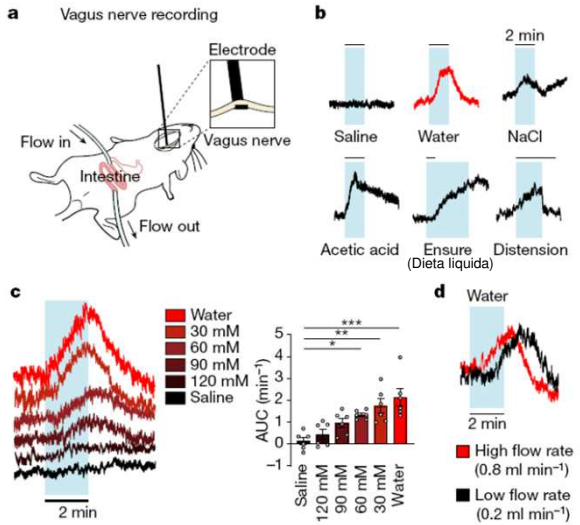
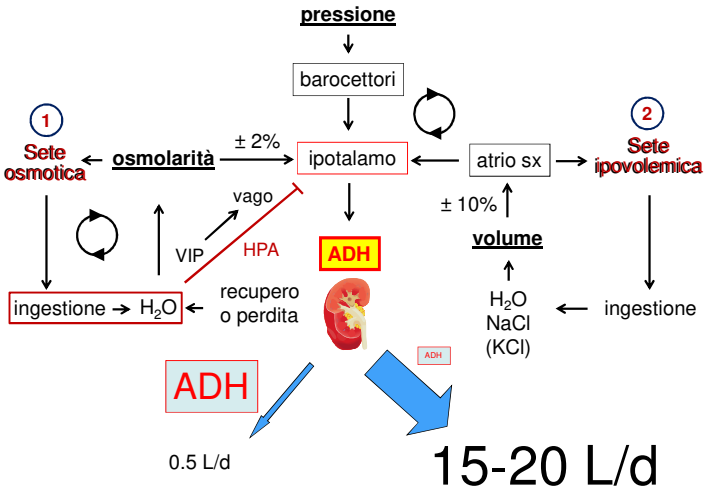


Fig. 1 | The vagus nerve responds to visceral osmolality changes. a, Diagram of electrophysiological recording of the vagus nerve. Electrical nerve activity was monitored during intestinal stimulation. **b**, Representative vagus nerve responses to intestinal infusion of isotonic saline, water, NaCl (1 M), acetic acid (4%), Ensure and intestinal distension (representative responses from 8 mice for saline and water, and from 6 mice for other stimuli). **c**, Dose dependence of osmolality responses. Representative integrated responses to 0–150 mM NaCl solutions (left) and quantification of responses (right) ($n = 6$ mice). **d**, Water response at different flow rates. Faster flow rate induced shorter latency but did not affect peak response amplitude (representative responses from 5 mice). Blue shaded areas denote infusion periods. AUC, area under the curve. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; Kruskal–Wallis test (with Dunn's post test). Data are mean ± s.e.m.

Because intestinal osmolality and nutrient detection cause various hormone secretions[29,30], we examined whether the hormonal signals are involved in HPA sensory functions. If this were the case, we would expect such a hormone to stimulate vagal neurons when infused into the HPV, and the hormonal response to be abolished after HVx. We found two categories of hormones that induced vagal activity. Peptide YY (PYY), cholecystokinin (CCK) and vasopressin (AVP) triggered robust responses, but the majority of responses remained after HVx (Fig. 5b, Extended Data Fig. 10a); by contrast, vasoactive intestinal peptide (VIP) and glucagon-like peptide-1 (GLP1) induced HPA-dependent responses—around 90% of vagal responses were abolished after HVx. If these hormones are involved in osmolality-induced vagal response through the HPA, their responses should overlap with the intestinal water response. Indeed, a considerable fraction (38%) of water-responding vagal neurons also responded to HPV infusion of VIP, but not GLP1 (Fig. 5c, Extended Data Fig. 10b, c). Of note, VIP responses selectively overlapped with water responses, but not with NaCl or glucose responses (Fig. 5c). These data support our idea that visceral hypoosmotic responses are, at least in part, mediated by VIP. Consistently, VIP levels in the HPV were significantly increased after spontaneous water intake (Extended Data Fig. 10d). Moreover, VIP-sensitive hypotonic responses were abolished in the presence of VIP receptor antagonist (Fig. 5d, Extended Data Fig. 10e), suggesting a role of VIP receptor (VIPR) in visceral osmolality sensing.

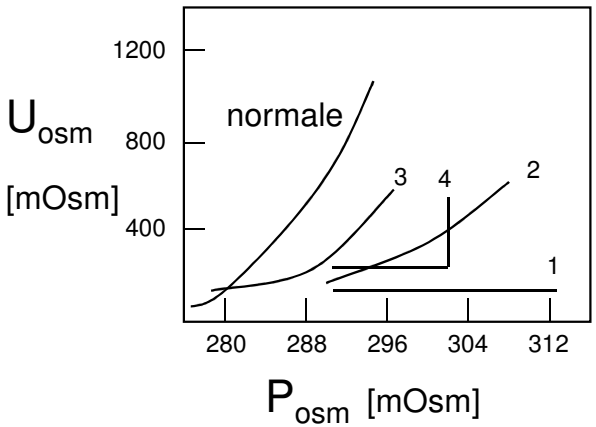


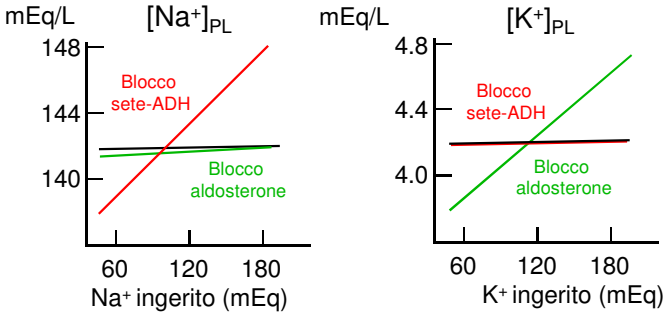
ADH

a. Carenza: diabete insipido
Triade: poliuria – sete – polidipsia

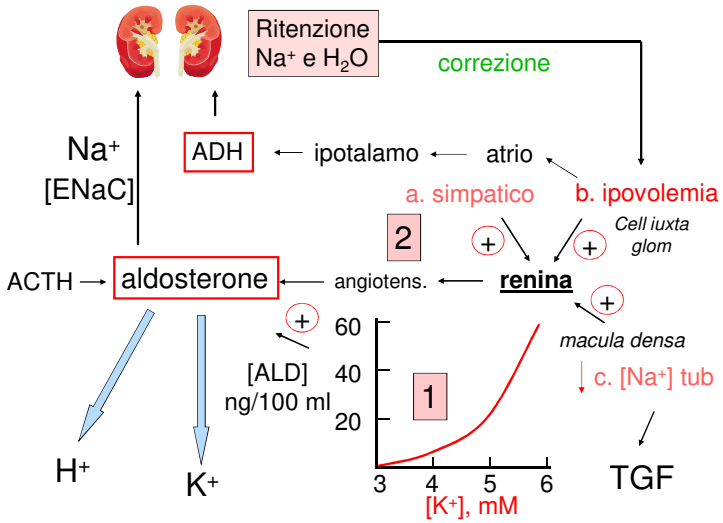
b. Eccesso: intossicazione da acqua

4 tipi di diabete insipido centrale





Alterazioni Sodiemia (osmolarità) [ADH]	Alterazioni Kaliemia [aldosterone]
• Ipernatriemia (diabete insipido) • Iponatriemia (tumori secernenti ADH)	• Iperkaliemia (ipoaldosteronismo) • Ipokaliemia (iperaldosteronismo)



ADH

a. Carenza: diabete insipido
Triade: poliuria – sete – polidipsia

b. Eccesso: intossicazione da acqua

Aldosterone

a. Carenza:

Ipoaldosteronismo I
(iperkaliemia & acidosi metabolica)

b. Eccesso:

Iperaldosteronismo I

(ipokaliemia, alcalosi metabolica, ipertensione)

Disidratazione (aumento sodiemia)

- Evaporazione eccessiva e/o mancata ingestione di acqua (naufragî, deserto)
- Ingestione di soluzioni saline ipertoniche (acqua di mare)

[A fini terapeutici]

- Infusione di mannitolo (trattamento dell'edema cerebrale)

Iperidratazione (diminuzione sodiemia)

- Sudorazione eccessiva con eccessiva ingestione di acqua