

Multifactorial control of water and saline intake: role of α_2 -adrenoceptors

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Abstract

Water and saline intake is controlled by several mechanisms activated during dehydration. Some mechanisms, such as the production of angiotensin II and unloading of cardiovascular receptors, activate both behaviors, while others, such as the increase in blood osmolality or sodium concentration, activate water, but inhibit saline intake. Aldosterone probably activates only saline intake. Clonidine, an α_2 -adrenergic agonist, inhibits water and saline intake induced by these mechanisms. One model to describe the interactions between these multiple mechanisms is a wire-block diagram, where the brain circuit that controls each intake is represented by a summing point of its respective inhibiting and activating factors. The α_2 -adrenoceptors constitute an inhibitory factor common to both summing points.

Key words

- Sodium intake
- Water intake
- Clonidine
- Noradrenaline
- Dehydration
- α_2 -Adrenergic agonist

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Mechanisms of hydrosaline intake and their inhibition by clonidine, an α_2 -adrenoceptor agonist

Water and sodium intake are ingestive behaviors important for the control of body fluid homeostasis. Both behaviors are critical for correcting the reduction in extracellular fluid volume, and water intake is also important for the correction of intracellular dehydration that ensues during an increase in body fluid osmolality.

The double-depletion hypothesis considers the water intake of water-deprived animals to be activated by a combination of signals derived from both intracellular and extracellular dehydration, which activates two separate pathways dependent on osmoreceptors and angiotensin II (ANG II), respectively (1). The osmotic pathway is probably

dependent on central acetylcholine (2). The inhibition of water intake dependent on each pathway by the α_2 -adrenergic agonist clonidine has suggested that both pathways converge to a final common pathway (3,4). Some of the many different forms of induction of water intake related to each pathway and inhibited by clonidine acting in the brain include increase in blood osmolality by administration of hypertonic solutions, direct cholinergic activation, direct angiotensinergic activation, and water deprivation (5-7). Meal-dependent water intake, which involves peripheral histamine (8) and probably central cholinergic receptors (9), is also inhibited by clonidine (10). Thus, clonidine is a ubiquitous inhibitor of thirst-inducing mechanisms. This inhibition is mediated by central α_2 -adrenergic receptors since it is antagonized by the α_2 -adrenergic antagonists yo-

himbine and idazoxan injected into the brain (5,11-13). Prazosin, an α_1 -adrenergic antagonist, also inhibits the effect of clonidine (5,12,13), but it can also bind to α_2 -adrenergic receptors (14). This observation, together with the effects of yohimbine and idazoxan, suggests that the receptors on which clonidine acts to inhibit water intake include α_2 -prazosin-binding sites.

The control of salt intake in the form of saline solution also involves more than one mechanism. Sodium depletion and the consequent volume contraction activate hormonal and sensory signals that in turn activate the central circuits of saline intake. These signals include ANG II and aldosterone (15) and reduction in the load of cardiovascular pressor receptors (16). The release of ANG II and reduction in the activity of pressor receptors are also involved in the activation of water intake (16). If sodium-depleted animals have access to water, reduction in blood osmolality also occurs, which in turn inhibits the central release of oxytocin, a component of inhibitory mechanisms of saline intake (17). Another form of saline intake is that expressed by normovolemic and normosodic animals. This intake is characteristically non-regulatory since it occurs in non-depleted animals. Its basis has not been systematically explored, but an interesting hypothesis is that it is controlled like circadian behaviors dependent on en-

dogenous clocks (18). Finally, saline intake is also induced by water deprivation (19), and although the mechanism is still not fully described, it probably involves ANG II (20). Interestingly, all these forms of saline intake are also inhibited by clonidine (10,21,22). This inhibition is also dependent on α_2 -adrenoceptors since it is antagonized by idazoxan and prazosin (13,22). The different models of water and saline intake inhibited by clonidine are listed in Table 1.

The mechanisms of action of clonidine on fluid intake involve at least the activation of α_2 -adrenergic receptors as discussed above. The circuit that mediates this inhibition is very probably specific for the behavior of water and saline intake since it is preferential for these forms of intake compared to solid food or sucrose solution (5,10). Other possible mechanisms are currently under investigation in our laboratory. Preliminary results suggest that the inhibition depends, at least in part, on the reduction of endogenous release of noradrenaline (23). Clonidine injected centrally also induces alterations in arterial pressure, but these alterations are not related to the inhibition of hydrosaline intake because similar alterations in arterial pressure are induced by other compounds, such as carbachol or isoproterenol, which do not affect water or saline intake (10,22). Another effect of clonidine is the induction of systemic release of atrial natriuretic peptide (ANP) (24). Interestingly, central ANP also inhibits water and saline intake (25), and, like central oxytocin, mediates osmotic inhibition of salt intake (26). An increase in blood ANP concentration is probably not the mediator of inhibition of fluid intake induced by clonidine since central cholinergic activation also induces the release of ANP (27), but this activation does not alter saline intake of water-deprived rats (20). Yet, a participation of ANP of central origin as a mediator of the effect of clonidine is a possibility to be tested.

Table 1 - Models of water and saline intake inhibited by clonidine.

Each model corresponds to at least one mechanism that induces water or saline intake and is inhibited by clonidine acting in the brain. Numbers in parentheses indicate the reference for each model in the text.

Water intake	Saline intake
Water deprivation (5,6,10,12,13)	Sodium depletion (10,13,22)
Cholinergic activation (6,7)	Water deprivation (22)
Angiotensin II (4,6,11,42)	Angiotensin II (21)
Cell dehydration (6)	Mineralocorticoid (21)
Meal associated (10)	Non-regulatory (need-free) (22)

A multifactorial model for dehydration-induced hydrosaline intake

One implication of the effects of clonidine on saline intake is that the concept of a final common pathway inhibited by α_2 -adrenoceptors (3,4) should include this behavior. However, since water intake and saline intake are distinct behaviors, it is not possible to assume a final common pathway for both of them. Therefore, there must be two central circuits that are activated by different types of dehydration and inhibited by α_2 -adrenoceptors, one for the control of water and the other for the control of saline intake. As mentioned above, these circuits share the activation by ANG II and by volume receptors during extracellular dehydration (1,15,16), but one (water) is activated (1,28,29) and the other (saline) is inhibited (17,30,31) by the increase in osmolality or in sodium concentration. Furthermore, aldosterone release activated by ANG II during

extracellular depletion but inhibited by the increase in osmolality (32) acts synergistically with ANG II in the brain to induce saline intake (15), in spite of the controversy on whether central or systemic ANG II is important for saline intake (15,33-36). Finally, the unloading of volume receptors probably removes the inhibition that hind-brain structures exert on water and saline intake (16,37,38). Every mechanism so far tested (Table 1) that induces water and saline intake is inhibited by clonidine. Therefore, these two behaviors share a common inhibitory factor represented by α_2 -adrenoceptors. The wire-block diagram shown in Figure 1 summarizes the connections between the multiple factors that control water and saline intake resulting from dehydration, and their relation to α_2 -adrenoceptors in the rat. The central circuits that control water and saline intake are represented separately, each corresponding to one summing point of multiple factors (variables) that con-

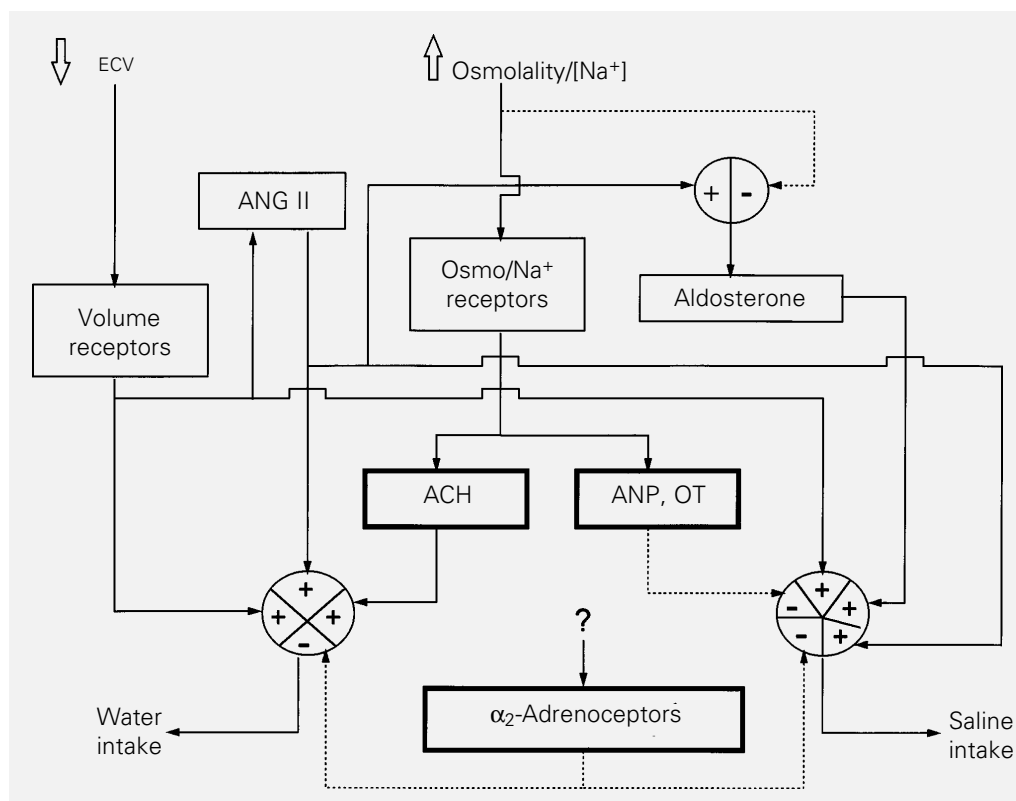


Figure 1 - Multifactorial block-diagram model of the control of water and saline intake. Central circuits that control water and saline intake and integrate the multiple inhibiting and activating factors described in the literature are represented by summing points (see text for references and discussion). Bold lines indicate central factors. Dotted lines indicate inhibiting and continuous lines indicate activating factors. Indents indicate bypass points. ECV, Extracellular volume; ACH, acetylcholine; ANP, atrial natriuretic peptide; OT, oxytocin; ANG II, angiotensin II (either central or peripheral).

trol each respective behavior. A summing point in the block diagram is represented by a circle receiving inputs from variables that can be added to or subtracted from the others (39). The central core of the diagram is the α_2 -adrenoceptor as a subtraction factor common to both summation points. The diagram of course does not intend to be definitive and still has points to be confirmed or modified. A question mark in the model exemplifies an important part to be understood, i.e., the mechanism of activation of α_2 -adrenoceptors in physiological situations. The diagram also does not include non-regulatory intakes or distinguish between central and peripheral ANG II acting in the brain.

Importance of the α_2 -adrenoceptors for the understanding of the role of noradrenaline in hydrosaline intake

The effects of clonidine described above suggest that endogenous noradrenaline acts on α_2 -adrenoceptors belonging to central inhibitory circuits that control water and saline intake. Noradrenaline injected into the brain inhibits water intake (10,40,41), but is also considered to be important for the activation of these behaviors.

Early studies have suggested opposite actions for alpha- and beta-receptors on wa-

ter intake, the first inhibiting and the second activating this behavior (41). Recently, a dual role for noradrenaline in water intake was proposed based on the opposite effects alpha-adrenergic antagonists (yohimbine or prazosin) had on water intake (42). When water intake was induced by water deprivation, yohimbine or prazosin inhibited the antidipsogenic effect of clonidine, but neither one injected alone altered water intake (5). When water intake was induced by ANG II, yohimbine or prazosin induced an inhibition of the behavior which was potentiated by clonidine (42). This potentiation suggests that clonidine and the antagonists act on receptors located at different sites and, therefore, that noradrenaline participates in one site that inhibits and in another that activates water intake. The importance of noradrenaline for the activation of water intake is confirmed by other studies utilizing alpha-antagonists or destruction of noradrenergic terminals (43-46).

Saline intake is also inhibited (10,21) or activated by noradrenaline (47). Thus, this double mediation of the control of water and saline intake by noradrenaline is explained by the dual-role hypothesis which proposes that central noradrenaline participates in the inhibition and activation of both behaviors (10,42,48).

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