Thirst and hydration: Physiology and consequences of dysfunction

Simon N. Thornton *

Université Henri Poincaré, Nancy Université, Nancy, France
INSERM, U961, Vandoeuvre les Nancy, France

A R T I C L E  I N F O

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A B S T R A C T

The constant supply of oxygen and nutrients to cells (especially neurons) is the role of the cardiovascular system. The constant supply of water (and sodium) for cardiovascular function is the role of thirst and sodium appetite and kidney function. This physiological regulation ensures that plasma volume and osmolality are maintained within set limits by initiating behaviour and release of hormones necessary to ingest and conserve water and sodium within the body. This regulation is separated into 2 parts; intracellular and extracellular (blood). An increased osmolality draws water from cells into the blood thus dehydrating specific brain osmoreceptors that stimulate drinking and release of anti diuretic hormone (ADH or vasopressin). ADH reduces water loss via lowered urine volume. Extracellular dehydration (hypovolaemia) stimulates specific vascular receptors that signal brain centres to initiate drinking and ADH release. Baro/volume receptors in the kidney participate in stimulating the release of the enzyme renin that starts a cascade of events to produce angiotensin II (AngII), which initiates also drinking and ADH release. This stimulates also aldosterone release which reduces kidney loss of urine sodium. Both AngII and ADH are vasoactive hormones that could work to reduce blood vessel diameter around the remaining blood. All these events work in concert so that the cardiovascular system can maintain a constant perfusion pressure, especially to the brain. Even if drinking does not take place ADH, AngII and aldosterone are still released. Furthermore, it has been observed that treatment of hypertension, obesity, diabetes and cancer can involve renin–AngII antagonists which could suggest that, in humans at least, there may be dysfunction of the thirst regulatory mechanism.

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mechanisms. The interplay between all these mechanisms gives a fascinating picture of physiological control. It would be too simplistic to say that mild, continuous, hypohydration, leads inevitably to dysfunction in several if not all of these regulatory systems and to a so called state of health needing medical intervention. It is, however, this hypothesis that I will explore here as it was first expressed at the IBRC conference on “Beverages and Health”, September 1–17, 2009. (For those readers who prefer a more traditional line of body fluid regulation then the following reviews are recommended [4–10].)

The regulatory system perhaps the most interesting to start with is thirst [11], a sensation that is difficult to describe [12], a physiological state that is often difficult to diagnose but a system that is very finely controlled. From his early work in rats James Fitzsimons (see review [13]) described two major thirst states, primary and secondary. The former being a state of physiological need and thus regulatory in nature, and the latter being not principally regulatory in nature.

Primary thirst was subsequently divided into that of intracellular origin and that of extracellular origin. But what is the meaning of this? All life depends on water and in animals this water, making up roughly 60 to 70% of our body mass, is distributed either inside or outside of the cells, i.e. throughout both the intracellular and extracellular compartments. This means that under ideal conditions, and I stress here ideal conditions where all physiological systems function correctly, the osmolality of all fluid compartments is the same and water is distributed proportionally (two thirds intracellular and one third extracellular). It is necessary here to introduce another element that plays a key role in the regulation of body fluids and that is the ion sodium. Sodium is the principal cation of the extracellular fluids (potassium being that of the intracellular compartment) and plays an essential role in the composition of the blood and thus the regulation of plasma osmolality, i.e. the gradient that regulates the movement of water within the body.

An increase in osmolality of the extracellular space (i.e. an increase in the concentration of sodium via, for example, a meal-induced addition of sodium) draws water from the intracellular space to reestablish the condition of equiosmolality. There exist neurons in the central nervous system (and possibly also in the periphery) that detect this increase in osmolality, the osmoreceptors [14–16]. Once stimulated (perhaps via a deformation of neuron size, thus acting like a mecano-receptor [17]) signal to other parts of the brain to initiate the act of searching for water (or a food with a large percentage of water) and then the behaviour of drinking. The water ingested is absorbed rapidly in the gut and should act to reduce osmolality to around the physiological set point i.e. between 280 and 300 mOsm/l.

At the same time as the search for water is initiated, and perhaps more importantly in the case where water is not found rapidly, the activated brain osmoreceptors stimulate magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus to liberate antidiuretic hormone (ADH or vasopressin) from their axon terminals in the posterior neurohypophysis into the blood stream [18,19]. The osmotic threshold for both thirst and ADH release is generally considered to be very similar if not identical. This liberated ADH then passes to the kidney where it stimulates, via a specific type 2 receptor mediated mechanism, aquaporin 2 accumulation in the outer wall of the collecting duct cells. This facilitates the passage of water down a concentration gradient across the otherwise impermeable wall into the medulla of the kidney for uptake by the blood, and thus reduces water loss.

Furthermore, there are specialized detectors in the top of the throat, the oropharyngeal receptors, which signal to the brain when water has been ingested [20]. Following a period of water deprivation, when ADH levels are increased, drinking of water in dogs and humans stimulates the oropharyngeal receptors which appear to signal the magnocellular neurons to reduce rapidly the release of ADH well before there was a decrease in plasma osmolality [21–23]. In humans this mechanism appears to be specific for water as the decrease in ADH is independent of fluid composition [24,25]. Furthermore, ratings of thirst have been shown to decrease also with drinking following a period of deprivation [26]. These effects have not been observed however in the rat [27,28], perhaps because it drinks at a much slower rate that humans or dogs. This could be seen as an efficient feedback mechanism to avoid any excess in ingestion (and in conservation through urine production). A considerable amount of overshoot could create a state of hypo-osmolality which is potentially dangerous leading initially to hyponatraemia, red cell lysis, then cell suffocation, as well as cerebral edema, balance disorders, coma and death (see fatal water intoxication [29]), as well as avoiding carrying excess to need weight in the form of water.

The released ADH has another action that of vasoconstriction, mediated via specific type 1 receptors located in the vasculature. In this particular example, in an ideal state, and an increase in osmolality from added sodium the vasoconstriction thus imposed would produce an increase in blood pressure from the increased blood volume due to the movement of water out of the cellular space into the extracellular space to reduce the osmolality. ADH has been shown also to reduce the thirst threshold to cellular dehydration [30]. This could be a physiological advantage to reduce the degree of dehydration and stimulate the search for water as soon as possible.

In the case where water is available to quench the induced thirst then the effect of the released ADH on blood pressure would be temporary. The ingested water would decrease plasma osmolality thus decreasing stimulation of the osmoreceptors and thus decreasing ADH release. The ingested water would produce an increase in blood volume which along with the decreased blood osmolality would induce water movement back into the intracellular compartment down a concentration gradient. The decreased levels of ADH would permit the blood vessels to relax, i.e. vasodilatation, and thus the increased blood volume would be accommodated thus restoration of all fluid volumes, blood pressure and osmotic levels to normal. Overall this is a very efficient mechanism in an ideal state.

As far as extracellular thirst is concerned, once again in an ideal state, fluid is lost initially from the vasculature (e.g. haemorrhage) leading to a decrease in blood volume. As the volume loss increases fluid would also move out of the interstitial compartment into the vasculature. The precise regulation of blood volume and blood pressure is rather complex and I will leave it for a future review. In the case here of thirst and fluid regulation it could be simplified initially to the control of blood volume. There are detectors in the arch of the aorta, carotid sinus and great veins for a decrease in volume that signal to the brain to initiate the search for water and to increase the release of ADH. The production of urine would thus be decreased in order to try and restore volume. To correctly restore volume sodium is also needed and these receptors could participate in the brain activation leading to the search for and ingestion of sodium, in other words a sodium appetite. At the same time the volume/pressure detectors in the juxtapglomerular apparatus of the kidney sense the decrease in perfusion pressure which stimulates the release of renin [31,32]. This enzyme acts on circulating angiotensinogen; an alpha2 globulin released from the liver, forming the decapeptide angiotensin I. Angiotensin converting enzyme (ACE) in the lung converts this to the octapeptide angiotensin II (AngII) that has several actions. It is vasoactive (causing vasoconstriction via an action direct and indirect on the vascular wall) thus reducing the diameter of the vasculature to encompass the lower blood volume and to facilitate blood flow, it stimulates the thirst centres in the brain to search out and ingest water, and it stimulates the release of the mineralocorticoid hormone aldosterone from the adrenals.

Aldosterone is the hormone of sodium regulation and it has two principle actions, one to increase sodium absorption in the kidney via an action in the distal tubule and collecting duct through stimulation of the sodium potassium ATPase pump, and the other to sensitise certain specific areas of the brain (especially the hypothalamus and hind brain) to the circulating levels of AngII, the combined effect of
which is to stimulate the search for and ingestion of sodium, i.e. to increase sodium appetite [33–35].

The ingestion of water and sodium together would restore blood volume to the initial values (see [13]). As blood volume increases the signals to stimulate thirst, ADH release and the release of renin (and thus AngII) would be decreased thus allowing the blood vessels to accommodate the increase in volume without producing an increase in blood pressure. An increased blood volume would permit increased perfusion of, and thus nutrient supply to, all tissues, especially the brain.

With thirst in general both intracellular and extracellular mechanisms are combined. Taking an experimental animal let us assume that it is euhydrated to start with and the source of water is removed from the cage. Through respiration and urine excretion initially the fluid reserves decrease resulting in an increase in osmolality of the extracellular compartment drawing water thus from the intracellular compartment and activating the osmoreceptors. The search for water is activated as well as the release of ADH to reduce urine water loss. Respiratory loss of water can be modulated by different animals but in the case here of the rat it is not reduced very much. Thus water movement from the intra to the extracellular compartment would not be sufficient to maintain blood volume and thus the volume receptors would be activated and renin released thus generating AngII. The combined vasoconstrictor action of AngII and ADH would ensure that the blood vessels were able to maintain blood pressure, and thus tissue perfusion pressure, especially that of the brain. With the AngII-induced release of aldosterone sodium losses would be reduced also and thus blood volume, and hence blood pressure and tissue perfusion, maintained for as long as possible.

The question arises as to the limit for survival as far as number of days is concerned without water. For lab animals as for humans it is about 4 to 5 days, and maybe 7 in the most ideal of conditions. Once water is made available then animals drink the required volume necessary to both restore osmolality to pre-deprivation values and along with the intake of sodium to restore blood volume [13]. As volume increases and osmolality decreases the circulating levels of ADH and AngII would decrease allowing the blood vessels to relax appropriately and thus able to accommodate the incoming volume of water and of salt. As has been noted previously ADH levels are appropriately and thus able to accommodate the incoming volume of water is made available then animals drink the required volume (based on increased plasma levels of AngII) that perhaps humans do not fully hydrate their fluid reserves. Let us start with children, from new born up through adolescence and their response to dehydration and hypovolaemia. For the most part they drink when given the opportunity but do not appear to fully replete their hydrational needs by drinking water or some other liquid [43–47]. From the description above of ideal physiology dehydration produces increases in blood osmolality, thus release of ADH, and if it is severe then the first defence against hypovolaemia starts with the release of AngII and hence aldosterone. The thirst thus activated should lead to increased water intake, reduction of osmolality and thus reduction in the release of the hormones. But does the stimulus of thirst in children always lead to water intake? To a fluid intake yes, and that could be to whatever is associated with drinking for the child, fruit juice or soda in French population). Several questions then need to be posed: 1) would this be enough to satisfy the deficit (taking into account that the oropharyngeal receptors would monitor ‘water’ content)? and 2) over the long term would this low level of water intake produce a state of low level dehydration and perhaps even hypovolaemia? These two conditions would thus produce a low level release of ADH, AngII and aldosterone. Both ADH and AngII are vasoactive, and AngII is permissive with the released catecholamines in the vascular wall which are also vasoactive. Over time, which could be 10, 20 or even 30 years, these effects could accumulate and most probably get worse as the level of “mild” dehydration in young adults would increase. The overall action of these vasoactive substances would be to slowly stiffen up the cardiovascular system [49], or make it less sensitive to a cycle of vasodilatation and vasoconstriction that should normally
follow the rising and lowering of the hormonal levels. A semi stiff vascular wall could make an ideal bed for the development of atherosclerosis. Vascular walls that change shape regularly would not normally allow the development of atherosclerotic plaques (Fig. 5).

To this particular pathophysiological state it would be appropriate now to add sodium. There is a physiological need for 2 to 3 g sodium per day yet today people in western societies appear to eat much more than this and there is a relation with this increased intake of salt to the generation of cardiovascular problems [50,51]. As stated above plasma levels of both AngII and aldosterone increase in response to hypovolaemia. Under normal physiological conditions high plasma sodium levels should inhibit the release of aldosterone through reduced levels of renin thence AngII due to increased blood volume [52,53]. Yet under conditions of hypovolaemia, despite high plasma sodium, aldosterone release would still be stimulated. As the stimulus is a decreased volume the released aldosterone would work to increase the reabsorption of sodium in the kidneys in order to try and restore the lost volume. My own work and that of others in rats have shown that aldosterone acts also on the brain (especially the hypothalamus and the nucleus of the solitary tract) in synergy with AngII to increase salt appetite [33–35,54]. These two actions would tend to increase osmolality leading to increased thirst and ADH release. As has just been suggested, humans do not appear to respond fully to thirst stimuli thus an inadequate volume of water would be
drunk, hormone levels would stay elevated, blood volume would tend to decrease and be contained in blood vessels unable to dilate to accept this increase in volume. Over time this could contribute to a slowly developing hypertension.

The treatment of hypertension has become a big industry (see [55]) with many drugs available on the market but those most used are the ones that are concerned with the renin–angiotensin–aldosterone system [56,57]. These medications can block the activity of the converting enzyme (with drugs like captopril, enanapril etc.) thus preventing the production of angiotensin I, or they block the specific AngII receptor type 1 (non-peptide antagonists such as losartan, valsartan, irbesartan etc.), or they block the aldosterone receptor [58]. Overall, this suggests that there is an increased activity of the renin–angiotensin–aldosterone system and it needs to be attenuated. However, as suggested above by the time a serious condition like hypertension is established many years of incorrect fluid intake could have probably gone on beforehand. Increased release of AngII would have maintained a vasculature in a semi-rigid state and thus allowed the development of perhaps a mild form of atherosclerosis thus preventing any real recovery when sufficient volumes are consumed. The body could thus be in a continual state of hypovolaemia. In this permanent state even decreasing the activity of the renin–angiotensin system is going to reduce a little of the hypertension, but it is not going to prevent the overall signal, hypovolaemia, that will persist and continue to

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**Fig. 4.** Normal thirst mechanisms with minimal drinking.

**Fig. 5.** Normal thirst mechanisms with appropriate hydration.
produce increased plasma levels of AngII. Furthermore, recent work suggests that antagonism of the renin-angiotensin system, at least in rat obesity models, can lead to a decrease in body weight through increased drinking [39].

Given a physiological system that responds appropriately to thirst stimuli then the problem of sodium becomes almost non important. Once ADH and AngII levels are regularly returned to baseline then liberation of aldosterone would be reduced and reabsorption of sodium reduced. Low levels of ADH, as is the case if all fluid compartments are filled, would lead to a low level diuresis and with this a natriuresis thus eliminating any excess to need sodium. Added to this equation is the consumption of fruit and vegetables, both a source of water as well, but mainly a source of potassium. Potassium supplementation in the diet has been shown also to play an important role in the reduction of hypertension [39].

There have been recommendations for the correct amount of water to be consumed per day [60] and the most recent comes from the Harvard Health Letter [61] where it reports that the Institute of Medicine suggests that for men it should be about 3.7 l of total water intake and for women 2.7 l. There has been some controversy over the previous recommendation of eight 8 oz glasses per day but in his 2002 article Professor Valtin [62] could not find good reason for this, nor for that matter any good physiological reason not to drink this much water. This same idea was taken up recently by Negoianu and Goldfarb [63] who underlined (author underlined).

Thus in conclusion, from a purely physiological point of view the regulation of thirst is absolutely necessary for the correct functioning of our milieu intérieur [64] and all the control systems that are implicated. Yet despite this humans appear to respond inappropriately to these thirst signals. This lack of appropriate fluid consumption appears to be associated with many of the serious health problems encountered today [39]. Several mechanisms have been proposed to account for this, one being AngII-induced metabolic dysfunction [65], another cell dehydration-induced metabolic dysfunction [66] and a third hypovolaemia-induced hypoxia with the consequence of mitochondrial dysfunction [67]. These serious health problems, which include obesity, diabetes, cancer and cardiovascular disease, all involve the renin–angiotensin–aldosterone system, blockade of which is reported to alleviate some of the symptoms [39,68–70]. Recently, the use even of antagonists of the ADH receptor has been advocated for certain types of cardiovascular pathologies [71,72], once again suggesting dysfunction of body fluid regulation.

It should not be forgotten though that increased drinking while good for overall health is going to depend on the age of the person concerned. Young people with only slightly developed cardiovascular pathology should be able to drink increased volumes of water without too much risk, although this remains to be determined. Elderly people, on the other hand, with well developed cardiovascular, plus other pathologies, would not be able to drink increased amounts due to perhaps the inability to accommodate this increased volume within the circulatory system. Any liquid that adds solutes that would increase plasma osmolality, albeit only temporarily, may not necessarily be of an advantage in a dysfunctional regulatory system. Most mineral waters on the other hand, although containing osmotically active solutes, are far less concentrated than plasma and thus should not pose a problem to hydromineral balance regulation even in a slightly dysfunctional state.

Therefore, in a society where we appear to consume more sodium physiologically necessary recommendations for humans to drink anything but water for liquid consumption will only further aggravate an already advancing pathophysiological state.

References

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