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THE CONTROL OF DRINKING

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Thirst is a sensation normally aroused by a lack of water and associated with a desire to drink water. The mechanisms involved in the control of drinking are useful to study, not only because of their clinical relevance, but also because the stimuli that lead to drinking can be identified, measured and manipulated, so allowing the basis of a relatively complex, motivated behaviour to be analysed.

Body water is contained within two main compartments. The intracellular water accounts for approximately 40% of body weight, and the extracellular water is approximately 20% of body weight, divided between the blood plasma, 5% of body weight and the interstitial fluid, 15% of body weight. After water deprivation, significant depletions of both the cellular and extracellular fluid compartments are found. To discover whether changes in either or both fluid compartments can act as stimuli for drinking, effects of selective depletion of one of the compartments on drinking, and the mechanisms activated, have been investigated as described below.

1 Cellular Stimuli for Drinking

The drinking that occurs when the body fluids become concentrated appears to be initiated by cellular dehydration, leading to cell shrinkage. Evidence for this is that the administration of concentrated sodium chloride solution leads to withdrawal of water from the cells by osmosis and produces drinking. The effective change appears to be cellular dehydration and not an increase in absolute osmotic pressure (i.e., osmolality, as measured by freezing point depression), in that administration of hypertonic substances such as sodium chloride and sucrose, which remain outside the cells and therefore cause cellular dehydration by osmosis, stimulates drinking. In contrast, similar concentrations of substances such as glucose, urea, and methylglucose, which cross the cell membrane and therefore do not lead to cellular dehydration, stimulate little or no drinking (Gilman, 1937; Fitzsimons, 1961a). Increases in sodium concentration rather than cellular dehydration could be the thirst stimulus (Andersson, 1978), but this seems unlikely since drinking follows the application of sucrose (which withdraws water from cells but does not raise sodium concentration) either directly to brain tissue (Blass & Epstein, 1971; Peck & Novin, 1971) or into the cerebral ventricles (Thrasher *et al.* 1980a). The degree of cellular dehydration must be monitored accurately, because sufficient water is consumed to dilute administered hypertonic sodium chloride solutions to the same concentration as the body fluids, that is to the same effective osmotic pressure (isotonicity). This relation is seen particularly clearly in animals in which excretion of the administered salt load by the kidneys is prevented (Fitzsimons, 1961a).

Cellular dehydration as a stimulus for drinking is sensed centrally, in the brain, rather than peripherally, in the body, because low doses of hypertonic sodium chloride (or sucrose) infused into the carotid arteries, which supply the brain, produced drinking in the dog. Similar peripheral infusions had no effect on drinking (Wood *et al.* 1977). The brain regions in which cellular dehydration is sensed and leads to drinking appear to be near or lie in a region extending from the preoptic area through the hypothalamus, and including tissue surrounding the anteroventral part of the third ventricle, to the zona incerta posteriorly. In these regions (but not in other brain regions) injections of small volumes of mildly hypertonic sodium chloride or sucrose lead to drinking, which at least at some sites is motivationally specific, as drinking, but not eating, is elicited (Blass & Epstein, 1971; Peck & Novin, 1971; Blass, 1974; Peck & Blass, 1975). Consistent with the hypothesis that these brain regions are involved in drinking in response to cellular dehydration, small lesions here can specifically impair drinking in response to cellular thirst stimuli yet leave drinking in response to other thirst stimuli intact, although more non-specific effects of the lesions are common (see Rolls & Rolls, 1981).

2 Extracellular Thirst Stimuli

Thus far we have considered only the effect of loss of fluid from inside cells on thirst. Although the amount of fluid in the extracellular fluid (ECF) compartment is less than that in the cells, it is vital for the organism that the ECF be conserved to avoid debilitating changes in vascular fluid volume and pressure. In addition to the physiological and hormonal mechanisms that contribute to the maintenance of the ECF volume (e.g. baroreceptor reflexes, antidiuretic hormone (ADH), and aldosterone), the behavioural response of drinking ensures that plasma volume does not fall to dangerously low levels.

The extracellular compartment has two components: the intravascular which contains the plasma, and the extravascular or interstitial fluid. These two components are in equilibrium and the receptors for controlling the ECF volume are located within the vasculature. ECF volume can become depleted in a variety of clinical conditions, which are accompanied by the loss of isotonic fluid as a result of vomiting, diarrhoea, or blood loss. Significant ECF volume depletion will cause the release of ADH, which will reduce renal fluid loss. There may also be a need to replenish lost fluid, and it is advantageous that thirst often follows the ECF depletion in these clinical conditions.

There are a number of ways that ECF volume can be depleted experimentally in order to study the role of ECF volume in thirst. Obvious methods include haemorrhage, lowering the sodium content of the diet and encouraging excessive sweating, urine production or salivation, depending on the species being tested. However, ECF can be removed quickly and simply by injecting high concentrations of colloids (gum acacia or

polyethylene glycol) either into the peritoneal cavity (Fitzsimons, 1961b) or subcutaneously (Stricker, 1968). Isotonic fluid accumulates around the colloid thereby depleting the ECF. Such depletion leads to a reduction in urine flow and an increase in water intake which is related to the magnitude of the depletion. Some hours after the onset of thirst, a marked appetite for sodium develops and the ingestion of sodium restores the volume and composition of the ECF to normal.

The drinking that follows ECF depletion could be mediated by receptors in the vasculature. The role of such putative receptors in thirst and ADH secretion can be studied by either constricting or expanding blood-vessels in regions where such manipulations would be interpreted as under- or over-filling. Such studies have indicated that the receptors for extracellular thirst are localized in two main regions of the vasculature, in and around the kidneys and the heart, as shown by the following evidence.

a *Role of the Kidney in Extracellular Thirst: the Renin–Angiotensin System*

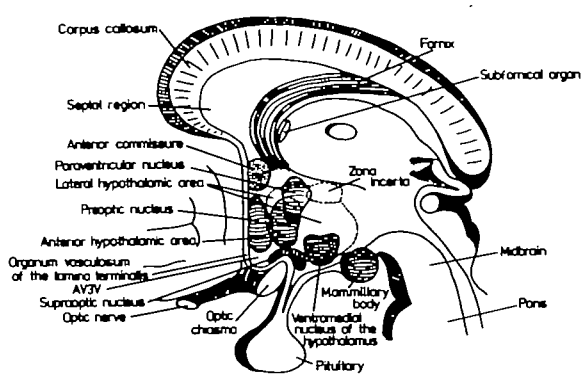
In the rat ligation of the inferior vena cava, which reduces venous return to the heart and reduces arterial blood pressure, leads to a marked increase in water intake and a positive fluid balance due to decreased urine flow. If both kidneys are removed before ligation, water intake is significantly reduced (Fitzsimons, 1964, 1969), which suggests that an essential thirst stimulus following caval ligation could be a reduction in blood pressure to the kidneys. In order to test this hypothesis, Fitzsimons reduced the pressure to the kidneys by partially constricting the renal arteries, and found that water intake increased. When reductions in blood pressure or volume are sensed by the juxtaglomerular apparatus in the kidneys, the enzyme renin is released. Renin acts on substrate in the plasma to form angiotensin I, which is converted to angiotensin II, a vasoactive octapeptide. Angiotensin II is an active dipsogen in that intravenous infusions stimulate copious drinking (Fitzsimons & Simons, 1969). The receptors for angiotensin-induced drinking are located in the central nervous system, since injections into localized brain regions of doses of angiotensin at least 1000 times smaller than those required peripherally stimulate rats in fluid balance to drink large quantities of water (Epstein *et al.* 1970). Not only is angiotensin very potent, it is also very specific. Drinking is the only behavioural response which follows its administration (Epstein *et al.* 1970; McFarland & Rolls, 1972; Rolls & McFarland, 1973) and this drinking is highly motivated (Rolls *et al.* 1972). A wide variety of species (including mammals, birds and reptiles) have been shown to drink following administration of angiotensin (see Rolls & Rolls, 1981).

Since the initial discovery that intracranial angiotensin stimulates drinking, much work has been aimed at localizing precisely the receptive site(s) in the brain. Angiotensin does not cross the blood–brain barrier, but the circumventricular organs, which are located on the surface of the cerebral ventricles, are outside the blood–brain barrier. Several circumventricular organs have now been suggested as receptive sites for angiotensin and one of these is the subfornical organ (SFO). Local application of angiotensin to the SFO in very low doses (1.0pg) can stimulate drinking, and lesions of the SFO or application to it of a competitive, angiotensin receptor blocking agent, at least in the rat, can abolish drinking in response to intravenous angiotensin without affecting drinking in response to cellular thirst stimuli (Simpson & Routtenberg, 1973; Simpson *et al.* 1977). The SFO has been shown electrophysiologically to contain angiotensin-sensitive units (Felix & Akert, 1974; Phillips & Felix, 1976), and anatomically to send projections to the medial preoptic area, the supraoptic nucleus, and the anteroventral part of the third ventricle (Miselis *et al.* 1979). Injections of low doses of angiotensin in the region of another circumventricular organ, the organum vasculosum of the lamina terminalis (OVLT) in the anteroventral part of the third ventricle (see fig. 1), also elicit drinking (Phillips, 1978). Relatively large lesions in this region, which included damage to fibres from the SFO, reduced drinking in response to angiotensin (and to hypertonic sodium chloride) (Buggy & Johnson, 1977; Thrasher *et al.* 1980b). This damage to SFO fibres may have been responsible for the reduction in angiotensin-induced drinking, since it was found that cutting the efferent fibres from the SFO to the anteroventral part of the third ventricle, which includes the OVLT, impaired drinking following administration of angiotensin (Eng *et al.* 1980; Lind & Johnson, 1980). Thus, while there is still controversy about the exact site(s) of action of angiotensin for eliciting drinking, there is reasonable evidence that there are specialized and localized regions of neural tissue in or near the SFO and the OVLT involved in drinking produced by angiotensin (see Rolls *et al.* 1980a; Rolls & Rolls, 1981).

b *Cardiac Receptors for Thirst*

Local changes in volume and pressure in and around the heart can affect the release of ADH, and receptors in this area could also be involved in extracellular thirst. Reducing the blood flow to the heart by partially constricting the thoracic inferior vena cava in the dog (a method used to produce low-output experimental cardiac failure) markedly increased water intake, which led to excessive oedema (Ramsay *et al.* 1975). Inflation of a balloon in the abdominal inferior vena cava also led to drinking which was correlated with the maximal fall in central venous pressure, but some drinking still occurred after administration of an angiotensin receptor blocking agent and presumably was mediated by cardiac receptors (Fitzsimons & Moore-Gillon, 1980). It is still not clear precisely where such cardiac receptors are located, but it seems most likely that they are in the low-pressure (venous) circulation around the heart, since the compliance of these vessels is high, making them responsive to changes in blood volume. It is thought that the information from these receptors is carried to the central

FIG. 1. Sagittal three-dimensional representation of the brain to illustrate some brain regions implicated in the control of drinking



AV3V: anteroventral region of the third ventricle

nervous system via the vagosympathetic nerves, which normally exert an inhibitory effect on thirst (Sobocinska, 1969; Fitzsimons & Moore-Gillon, 1980).

3 Control of Normal Drinking

It has been shown above that there are mechanisms by which depletion of the cellular or the extracellular fluid compartments can stimulate drinking. An important question is to what extent these mechanisms are normally activated during thirst and drinking, whether produced by water deprivation or occurring when there is free access to water. Perhaps habit is one factor normally important in the initiation of drinking, but are deficits in the body fluid compartments normally involved in the initiation of drinking?

To gain evidence on this, it is first important to know whether deficits in the body fluid compartments are produced, for example, by water deprivation. There are deficits in both fluid compartments produced by water deprivation, and their extent in four different species including man is shown in Table I. Next, it is found that the deficit in the cellular fluid compartment is large enough to lead to drinking, as shown by threshold measurements determined for the initiation of drinking in response to cellular dehydration. For example, following infusions of sodium chloride in the monkey, the threshold increase in plasma concentration necessary to evoke drinking was found to be 7 mOsmol/kg H_2O, which was less than the increase produced by water deprivation for 24 hours (R J Wood, E T Rolls and B J Rolls, in preparation). Other evidence comes from repletion experiments. When, after water deprivation, intravenous water preloads were given which effectively abolished the cellular fluid deficit, drinking was reduced by 65% in the rat (Ramsay *et al.* 1977a) and by 85% in the monkey (R J Wood, E T Rolls and B J Rolls, in preparation). In the dog, selectively rehydrating central receptors for cellular thirst through intracarotid infusions of water, reduced drinking by 72% (Ramsay *et al.* 1977b). If the ECF deficit is corrected by intravenous infusions of isotonic sodium chloride, then drinking is reduced by 27%, 20% and 5% in the dog, rat and monkey, respectively (see Rolls *et al.* 1980a). Thus depletion of the fluid compartments is an important determinant of drinking after water deprivation, with the depletion in the cellular compartment being more important, particularly in the primate (see further Rolls & Rolls, 1981).

There are less comparative data available on the importance of fluid depletions for drinking when free access to water is allowed. In the dog the threshold for cellular dehydration to induce drinking (measured using intravenous sodium chloride infusions) was exceeded before normal drinking (Rolls *et al.* 1980a; R J Wood & B J Rolls, in preparation). Thus for normal drinking with free access to water, sensed deficits in the body fluid compartments may be important in the initiation of drinking, but more species need to be studied in this context.

4 Maintenance and Termination of Drinking

Drinking still occurs when ingested water is allowed to drain from a fistula in the oesophagus, stomach or duodenum. This is found in the rat, dog and monkey (see Rolls *et al.* 1980a; Rolls & Rolls, 1981), and indicates that animals drink in order to obtain oropharyngeal (and other pregastric) sensations such as the taste of water, at least in the first instance, although the effect may be modified by learning. In fact, even a small quantity (e.g. 0.1 ml) of water delivered orally is sufficient to reinforce drinking, whereas much more water (e.g. 1–2 ml) must be delivered for the rat to learn a response in order to deliver it intragastrically (Epstein, 1960) or intravenously (Nicolaidis & Rowland, 1974). This underlines the importance of exteroceptors in detecting and responding correctly to the presence of water, and shows that the presence of water in the gut or the dilution of plasma are not the primary sensations which control the animal's drinking. A subjective analysis of the oropharyngeal control of drinking found that humans report (using a quantitative visual analogue rating scale) that the pleasantness of the taste of water is increased when they are thirsty as a result of water deprivation for 24 hours, relative to the non-deprived condition (Rolls *et al.* 1980b). It thus appears that oropharyngeal factors such as taste and swallowing maintain drinking and provide the incentive for drinking.

Oropharyngeal factors are of less importance, and gastric and post-gastric factors such as gut stimulation by water, and the systemic effects of absorbed water, are more important in the termination of drinking. If, for example, drinking is measured with an oesophageal, gastric or duodenal fistula open, then much more water (e.g. 1.5–10 times) is consumed than normally or when the fistula is closed (Maddison *et al.* 1980a; Rolls *et al.* 1980a). Gastric distension appears to be one factor in satiety, for if drinking is allowed to terminate normally in the monkey, and then a gastric cannula is opened to allow water in the stomach to drain out, drinking starts again very promptly (Maddison *et al.* 1980b). Gastric distension can only operate normally if ingested water reaches the intestine to inhibit gastric

TABLE I. Changes in body fluid variables produced by water deprivation in four species (Based on Rolls *et al* 1980a)

	Rat (n 15)	Dog (n 8)	Monkey (n 5)	Man (n 5)
Osmolality (mOsmol/kg H_2O)				
Non-deprived	299 6 ± 0.5	298 5 ± 0.7	297.8 ± 2.4	282 4 ± 2 2
Deprived	306 1 ± 0.6***	310 3 ± 0.9***	311 0 ± 4.5***	290 3 ± 1.8***
Sodium (mEq/l)				
Non-deprived	138.9 ± 0 5	147.3 ± 0 7	143 0 ± 1 7	140 4 ± 0.7
Deprived	139 9 ± 0.5	153 7 ± 0.7***	149.2 ± 2.0***	143.3 ± 0 6***
Haematocrit reading (%)				
Non-deprived	42.2 ± 0 7	42.4 ± 2 0	36 6 ± 1.9	47 2 ± 1 8
Deprived	46 2 ± 0.6***	47 3 ± 2 1***	35.8 ± 1.1	48 2 ± 2.3
Plasma protein (g%)				
Non-deprived	7 5 ± 0 2	5.5 ± 0.1	7.1 ± 0 2	7.3 ± 0.2
Deprived	7 8 ± 0.1***	6.1 ± 0.1***	7 4 ± 0 2	7 7 ± 0 2***

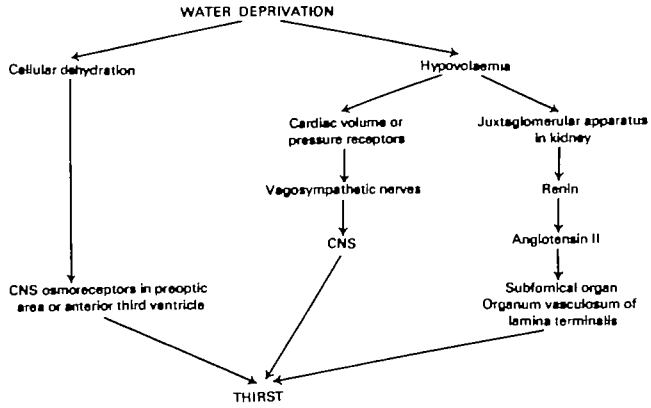
The means (± s.e.m.) are shown for plasma osmolality, sodium concentration, haematocrit reading and protein concentration, measured before and after deprivation. Osmolality and sodium provide indices of cellular dehydration. Haematocrit reading and plasma protein indicate changes in plasma volume. The periods of water deprivation (with food available) were 21 hours for the rat and 24 hours for the dog, monkey, and man. Significant differences between pre- and post-deprivation values are indicated *** $P < 0.001$

emptying, because excessive drinking occurs with a duodenal fistula open (Maddison *et al.* 1980a). Gut stimulation by water, and possibly activation of immediately post-absorptive hepatic–portal mechanisms, may also contribute to satiety, because intraduodenal infusions of water are relatively more effective in terminating drinking than intravenous infusions (Wood *et al.* 1980). In the monkey and other relatively rapid drinkers such as the dog and man, systemic dilution produced by ingested water is not rapid enough to account for the termination of drinking although, within 15–20 minutes after access to water, dilution of the body fluids is occurring. This dilution does at least contribute to satiety, since equivalent dilution produced by intravenous infusions of water reduces drinking (Wood *et al.* 1980). The termination of drinking is best considered as the sequential activation of a number of contributing factors, starting with oropharyngeal stimulation by water (which appears to make a partial contribution to satiety as shown by observations that drinking with an oesophageal fistula open does usually stop in very rapid drinkers such as the dog: Towbin, 1949), gastric distension (which humans report subjectively to occur rapidly as satiety develops: Rolls *et al.* 1980b), gut and hepatic–portal stimulation by water, and finally systemic dilution and expansion (see Rolls *et al.* 1980a; Rolls & Rolls, 1981).

5 Conclusions

Drinking can be initiated by depletion of either the cellular or extracellular fluid compartments. Both cellular and extracellular thirst stimuli (i.e., cellular dehydration and hypovolaemia) are produced by water deprivation in a variety of mammalian species, including man. Experiments in which the deficits in the fluid compartments are selectively repleted indicate that changes in both compartments contribute to drinking following water deprivation, but that changes in the cellular compartment are the more important. A summary of the mechanisms thought to be involved in drinking after water deprivation is shown in fig. 2.

FIG. 2. A summary of the controls of drinking after water deprivation



There is some evidence that in the dog the initiation of spontaneous drinking when water is freely available is due to plasma changes. Comparable experiments to determine to what extent normal drinking in other species may similarly be due to physiologically detected fluid deficits, or may be in anticipation of, or in addition to, such needs have not yet been performed. Drinking is maintained or reinforced by oropharyngeal factors such as the taste of water, and it appears that the pleasantness of the taste of water in man is influenced by the degree of thirst. When water is consumed, the following changes occur in sequence and all contribute to the termination of drinking: oropharyngeal stimulation by water, gastric distension and gut stimulation by water, and finally systemic dilution.

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