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The interaction of meal-related, rhythmic and homeostatic mechanisms and the generation of thirst and drinking

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Abstract

One of the primary goals of the study of thirst is to understand why drinking occurs under *ad libitum* or natural conditions. An appreciation of the experimental strategies applied by physiologists studying thirst from different perspectives can facilitate progress toward understanding the natural history of drinking behavior. Drinking research carried out using three separate perspectives – homeostatic, circadian rhythms, and food-associated – generates types of information about the mechanisms underlying drinking behavior. By combining research strategies and methods derived from each of these approaches, it has been possible to gain new information that increases our appreciation of the interactions between homeostatic mechanisms and circadian rhythms in the modulation of water intake and how these might be related to drinking associated with food intake under near natural conditions.

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- Meal-related drinking

Drinking or the ingestion of water is a necessary behavior for maintaining hydration and hence survival in many species. Understanding why and when animals drink under normal or natural conditions is a primary goal of many physiological researchers with different theoretical and methodological approaches. It is possible to divide physiological research on water intake into three areas: 1) the study of drinking as a homeostatic response, 2) the study of drinking as an index of circadian rhythms, and 3) drinking that is associated with other periodic behaviors or physiological responses such as food intake.

The physiological basis of drinking induced by homeostatic challenges, involving both disruptions in osmolality and extracellular fluid volume, has been studied extensively. Hyperosmolality, induced by injection of hypertonic saline, activates osmoreceptors. Evidence indicates that osmo- or sodium-receptors are present both peripherally in the hepatoportal system and centrally as specialized neurons located in several areas of the brain. The best information about the nature of signal transduction in osmoreceptors is available for central receptors. These osmoreceptors are sensitive to changes in osmotic pressure that produce changes in cell volume which in turn deform the cell membrane to open stretch-activated ion channels (1).

Hypovolemia and hypotension result in the activation of both peripheral and central receptors. In this case, the peripheral recep-

tors are the baroreceptors located on both the low and high pressure sides of the circulation. These receptors send afferents to the brain via the vagus and glossopharyngeal nerves (2). Evidence indicates that these cells are also stretch-receptors with stretch-activated ion channels, but in this case, the nerve endings respond to shear stress caused by deformation of blood vessels or of the chambers of the heart.

Another form of signal to the brain associated with hypovolemia/hypotension is derived from increased levels of circulating angiotensin II (ANG II). Plasma levels of ANG II are determined by the release of renin from sympathetic activation and from a renal baroreceptor mechanism (3). Evidence indicates that circulating ANG II levels are sensed centrally by the subfornical organ (SFO), a structure which has no blood-brain barrier. Efferent pathways from the SFO activate several brain loci functionally implicated in the regulation of body fluid homeostasis (4).

In comparison to the homeostatic controls of drinking, much less is understood about the physiological basis of circadian influences on water intake. This is mainly because the periodicity of drinking has been used more as a dependent variable reflecting activity of the circadian system (i.e., a marker) rather than a direct topic of research. However, much information on the neural pathways and structures controlling mammalian circadian rhythmicity, in general, is known. Circadian rhythms in mammals are controlled by a primary endogenous oscillator in the hypothalamus, the suprachiasmatic nucleus (SCN; 5). Rats deprived of a near-24-h external signal (e.g., light onset) but with an intact SCN still drink with a rhythmicity of close to 24 h (i.e., a "free-running rhythm"; Figure 1). When exposed to an external Zeitgeber, such as a near-24-h light-dark (LD) cycle, the free-running drinking rhythm of rats synchronizes (entrains) to the external

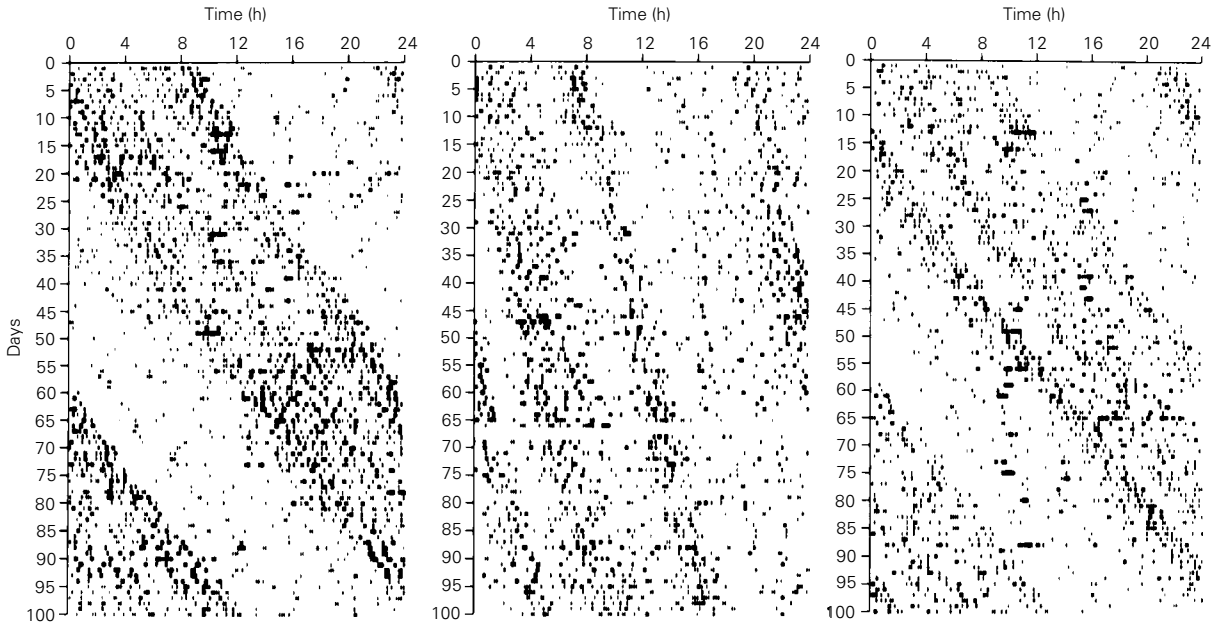

Figure 1 - Three representative drinking actograms of rats during the course of the study. Stable free-running rhythms are evident in all records. However, the first and third records are examples from rats that had free-running periods long enough to allow adequate sampling across circadian phases. The second record is from a rat whose data were excluded from analysis because the period of its free-run did not allow sufficient sampling of different phases of its circadian rhythm. Quantitative measures of water intake after hypertonic saline (Figure 2) are based on data obtained from inverted graduated cylinders. Actograms were only used to derive circadian time of injections. For this, the onset of drinking activity was defined as circadian time 12. (Reprinted with permission from Ref. 17).

stimulus. Such entrainment is thought to be mediated by a direct retinohypothalamic projection to the SCN as well as a secondary pathway via a retinal projection to the intergeniculate leaflet of the lateral geniculate complex. The cells of the intergeniculate leaflet in turn may influence the SCN, especially the direct retinorecipient area of the ventrolateral SCN, via a direct geniculohypothalamic tract and via a projection to the contralateral intergeniculate leaflet (6). Ablation of the SCN results in an abolition of drinking rhythms regardless of whether they are diurnally entrained or circadian free-running. However, rhythmicity in some circadian-associated variables (e.g., temperature) may persist after SCN ablation suggesting possible secondary endogenous oscillators (7). Given the large number of circadian variables that are affected by the SCN, this nucleus has a surprisingly small number of output pathways. The largest projection of the SCN is to the subparaventricular zone, and this area has been proposed as an important component of a modulatory circuit that influences many circadian variables (8).

The third and most poorly understood aspect of the control of drinking is the physiological link between food intake and water intake. If one is to understand the "normal" physiological controls of drinking, this area of research may be actually the most germane. In rats, "normal" water intake is temporally and quantitatively associated with food intake, both in terms of the daily nocturnal pattern (9) and in terms of individual bouts of eating. In rats, most water intake is associated with feeding bouts; about 75% of daily water intake occurs within 10 min before, during, and 30 min after a bout of feeding (9). The amount of water consumed correlates positively with the quantity of food ingested (9,10). Thus, arguments can be made that food intake controls water intake (but see Ref. 9 for arguments that food intake cannot explain all the rhythmic aspects of drinking).

Homeostatic researchers have argued that the above associations can be explained by a "homeostatic hypothesis". Theoretically, food intake will produce both hyperosmolality (via intake of salts or proteins) and hypovolemia (via movement of extracellular fluids into the gut for digestion). Indeed, this can be demonstrated under experimental conditions (11,12). However, the problem may be that the experimental challenges that evoke drinking are often selected to demonstrate a strong effect rather than to show what may occur "naturally". The critical factor of the latter point rests on timing. Do homeostatic deficits after food intake occur soon enough to explain the onset of water intake under natural (i.e., *ad libitum*) conditions? Alternatively, one could argue that mechanisms activated by most homeostatic challenges are extreme responses initiated under pathological conditions (e.g., hemorrhage). However, in the typical laboratory situation of *ad libitum* food and water access, the association between eating and drinking may be more dependent on mechanisms activated prior to homeostatic deficits. Kraly (12) has demonstrated through an elegant series of studies that "pre-homeostatic" drinking may involve preabsorptive release of histamine and activation of osmo- or sodium hepatoportal receptors (13). Of interest to the present discussion, histamine may produce a pre-homeostatic activation of the renin-ANG II system (14) and visceral afferents from the liver or hepatoportal system may signal impending systemic dehydration.

Although each of the three approaches to the study of thirst is robust in its own right, it is reasonable to ask what is the most valuable insight that can be derived from such diverse approaches to thirst research that will help explain water intake in rats. Paraphrasing Moore-Ede (15) from a highly illuminating lecture presented a decade ago, one scientist's data is the other's noise. That is, homeostatic researchers have avoided the

problem of circadian "noise" in their experiments by conducting their studies at the same circadian time each day. Circadian researchers largely have ignored the fact that drinking is influenced by homeostatic factors, and researchers examining the relationship of eating and drinking have failed to explain diurnal variation. In this light, we have attempted a more integrative approach in some of our studies on analysis of the interactive controls of drinking in rats. That is, we have tried to understand how circadian factors interact with homeostatic and food-related drinking. These studies have demonstrated that when either hyperosmotic or hypovolemic thirst challenges are administered to rats, the amount of water intake is affected by the phase of the LD cycle of the challenge (16; also see below for discussion of other studies that failed to detect an LD modulation). The LD modulation of water intake has been subsequently shown to be a truly circadian effect and not merely a direct "masking" effect of the light (since light may inhibit behavior of nocturnal rodents). This was accomplished by demonstrating that there is also a phasic modulation of drinking in response to homeostatic challenges under free-running conditions (Figures 1 and 2; 17). The major conclusion from these two studies is that the behavioral response to homeostatic challenges is not a constant function of the intensity of the challenge but is modulated in a non-additive manner by the circadian phase of the rat (other studies indicate non-additive modulation of factors involved in body fluid/mineral homeostasis; reviewed in Ref. 15).

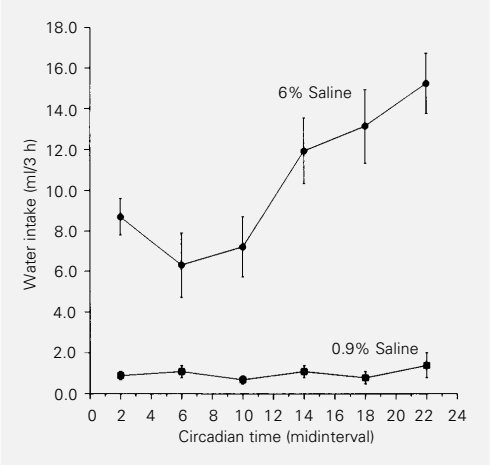

Figure 2 - Three-hour mean water intake (midpoints of 4-h bins) for 9 rats after injections of either 6% or 0.9% saline. Data were obtained in tests involving free-running rats and then reordered in circadian time based on circadian time when injection occurred for each individual. Circadian time 12 is onset of activity. (Reprinted with permission from Ref. 17).

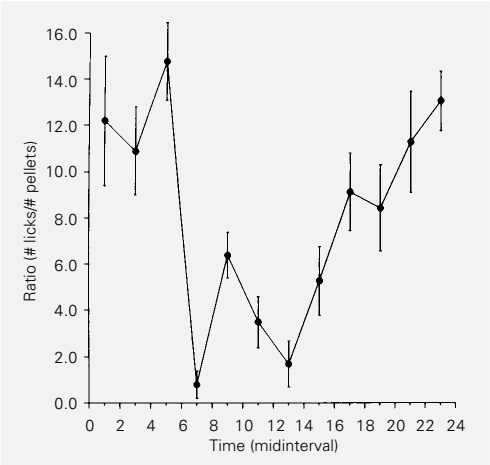

Figure 3 - Mean ratios of water intake to food intake for 9 rats receiving bihourly meals where each is equal to 1/12 of 80% of their daily intake under *ad libitum* feeding conditions. Light onset of 12:12-h LD cycle is at 0600. (Reprinted with permission from Ref. 18).

In further studies, we examined a more "natural" type of induced water intake by studying drinking associated with food intake. Initial studies showed that under LD conditions a disproportionate amount of water intake is associated with food intake in the dark compared to the light phase (9). One problem which became apparent when conducting the latter study was that the rat eats very little food during the light phase. This problem was obviated in an additional experiment which abolished the feeding differential between the rat's light and dark phases. This was accomplished by offering equally sized bihourly meals to the rats across the 24-h day (i.e., a forced abolition of the feeding rhythm). Under this condition, the rats demonstrated a dramatic diurnally dependent change in the amount of water intake following the ingestion of relatively constant-sized meals (Figure 3; 18). Although we cannot unequivocally state that the latter is a circadian modulation, the results of the direct homeostatic challenges under free-running conditions would support such a conclusion. The latter two studies argue that

food intake does induce water intake, but whatever the mechanism – homeostatic or pre-homeostatic – it is modulated by the phase of the circadian system.

The above observations have led us to formulate the *circadian modulation* hypothesis: both the homeostatic and pre-homeostatic mechanisms of induction of water intake in rats are mechanistically affected by the circadian oscillation of the physiological status of the organism. Either there is a direct change in gain of central mechanisms of fluid balance, or the modulation is an indirect reflection of a change in amplification from peripheral factors.

A further hypothesis that may be offered as a broad extension to explain the relationship of the three areas of drinking research is the idea expressed by Kraly (11) that under natural conditions, food intake induces a cascade of physiological signals. First, food elicits a pre-absorptive histamine release which may provide a pre-homeostatic activation of the renin-angiotensin system (14). There may be additional pre-homeostatic activation of the latter system via anticipatory conditioned responses (19). Further activation of the ANG II system may occur later as a result of hypovolemia as a consequence of sequestration of extracellular fluid in the gastrointestinal tract. Lastly, the movement of ions or proteins into the circulation may provide an osmotic stimulus for drinking, first at the peripheral level via afferents from the hepatoportal system (pre-homeostatic) and finally at the level of dehydration of the brain (an event that evolution has probably programmed as the last defense). Circadian modulation of the cascade may take place at several levels. The critical question will be to determine where and how such modulatory influences are exerted.

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