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Physiological state tunes mesolimbic signaling: Lessons from sodium appetite and inspiration from Randall R. Sakai*

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Abstract

Sodium deficit poses a life-threatening challenge to body fluid homeostasis and generates a sodium appetite - the behavioral drive to ingest sodium. Dr. Randall R. Sakai greatly contributed to our understanding of the hormonal responses to negative sodium balance and to the central processing of these signals. Reactivity to the taste of sodium solutions and the motivation to seek and consume sodium changes dramatically with body fluid balance. Here, we review studies that collectively suggest that sodium deficit recruits the mesolimbic system to play a role in the behavioral expression of sodium appetite. The recruitment of the mesolimbic system likely contributes to intense sodium seeking and reinforces sodium consumption observed in deficient animals. Some of the hormones that are released in response to sodium deficit act directly on both dopamine and nucleus accumbens elements. Moreover, the taste of sodium in sodium deficient rats evokes a pattern of dopamine and nucleus accumbens activity that is similar to responses to rewarding stimuli. A very different pattern of activity is observed in non-deficient rats. Given the well-characterized endocrine response to sodium deficit and its central action, sodium appetite becomes an ideal model for understanding the role of mesolimbic signaling in reward, reinforcement and the generation of motivated behavior.

Keywords

Dopamine; Motivation; Reward; Nucleus accumbens; Sodium appetite; Homeostasis

Randall Sakai was my first academic colleague. I say this because he had no cause for a stake in my development as a scientist. He was not my boss nor was he an official academic mentor of mine. I met Randall just after starting a position as a laboratory technician in the lab of Dr. Harvey Grill at the University of Pennsylvania. I was 22 years old and knew nothing of the world of academia. Randall, with no self-interest what-so-ever, gleefully took it upon himself to help me feel comfortable in my new surroundings. He also educated me – teaching me what grants were all about and how students progress through academia. He took me fishing and taught me about sushi, the work of Alexander Calder and countless other aspects of life in which the typical 22-year-old fresh out of college is

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deficient. As I grew as a scientist, Randall challenged me and helped me to hone my arguments. He took delight in introducing me to leaders in the field of ingestive behavior. He danced at my wedding, cared about my children and was a champion of my career. I was not alone in these experiences and I know that many are grateful for Randall's influence. I will always remember and be most grateful for Randall's sharp wit, keen eye for data, its implications, explanatory power and limits, but just as much for his enjoyment of life, revelry in the success of others and genuine friendship.

[~MFR]

1. Sodium appetite as motivated behavior

The survival of living beings is dependent on the monitoring of internal body state and compensatory homeostatic regulation. In the age of the obesity epidemic, much attention is rightly focused on the neural and endocrine systems that drive feeding upon caloric deprivation and terminate feeding upon satiety. Understanding how these processes become altered to permit obesity is necessary to reverse the pervasiveness of obesity and its comorbidities. Chronic dysregulation of body fluid homeostasis also has associated disease states. Congestive heart failure greatly contributes to heart disease, the leading cause of death in the United States [1,2]. Furthermore, challenges to body fluid homeostasis pose dire threats to survival including dehydration and hyponatremia – certainly more immediately than caloric deficit [3]. Thus, in both diseased and healthy individuals, body fluid homeostasis remains paramount for survival.

Body fluid homeostasis requires tight regulation of both body fluid volume and composition – primarily through the consumption of water and sodium but also through excretory mechanisms. Dr. Randall R. Sakai dedicated a substantial portion of his career to understanding the hormonal signals that arise from negative sodium balance and how those signals interact with the central nervous system to drive sodium intake – a phenomenon known as sodium appetite. Randall, together with his student Eric Krause, drafted a beautiful review of sodium appetite as an homage to the revolutionary work of Curt Richter, who first described sodium appetite in 1936 [4,5]. Randall and his co-authors over the years have focused on the hormonal responses to sodium depletion and the integration of these signals by central circuits to generate compensatory physiological processes and behaviors. Randall greatly contributed to our understanding of how mineralocorticoids and glucocorticoids interact in the service of sodium appetite [6–8]. This brief review is not meant to extensively cover the sensing of sodium deficit. For this, the reader is strongly encouraged to seek out Randall's work as well as reviews [4,9–11] and books [12,13] written by others. Instead, we aim to honor the work of Randall Sakai by briefly reviewing studies that investigate the drastic changes in motivation that are characteristic of sodium appetite and the neurobiological underpinnings of the drive to consume sodium in a sodium deficient state.

Sodium deprivation and depletion produce a powerful, specific and innate appetite for sodium which promotes appetitive and consummatory behaviors directed towards sodium-containing substances (e.g. sodium chloride, NaCl). In a laboratory setting, sodium deplete animals preferentially ingest solutions containing the sodium ion and no prior experience

with sodium-containing solutions is required for this to occur [14,15]. The sodium ion of a NaCl solution is detected by taste mechanisms [16–19] which allow for the immediate discrimination of salt solutions and selective consumption of only those which satisfy the need state of the animal. Interference with sodium taste transduction mechanisms (through blockade of lingual sodium channels or transection of cranial nerves which relay gustatory information to the brain) essentially eliminates the expression of a sodium-selective appetite [16,20]. The taste of sodium, therefore, drives the intake behavior that is necessary to replenish internal sodium deficit.

The value of the taste of sodium is highly dynamic. Hypertonic, concentrated sodium solutions are avoided by sodium replete animals [15]. However, in a sodium deplete state, the taste of concentrated NaCl becomes transformed to one that is appetitive, palatable [21] and reinforcing [15,22]. In this way, the value of sodium solutions changes dramatically with physiological state, making sodium appetite an ideal model for exploring the central systems that influence value assignment, goal-directed behavior and reinforcement.

The reinforcing nature of sodium for sodium deplete rats was noted in several early studies and has been replicated many times over. Consumption of NaCl [14] and average lick rates for a hypertonic NaCl solution [15] greatly increase with sodium depletion. This increase in intake behavior is not a consequence of a reflexive response but is instead indicative of voluntary motivated behavior. Indeed, sodium deplete rats will make operant responses for access to sodium [22–24], will increase running speed down a runway to obtain a sodium reward [25] and will display approach behavior towards cues associated with sodium availability [26,27]. Insight into the neural machinery required for these motivational processes was gained through work with chronic supracollicular decerebrate (CD) rats that had a severed connection between the forebrain and caudal brainstem [28]. Similarly to intact rats, CD rats concentrate their urine after hypertonic sodium injection; demonstrating some intact responses to challenges of body fluid homeostasis. However, CDs, unlike intact rats, fail to increase both intake of hypertonic sodium and appetitive responses to the taste of hypertonic sodium following depletion [29]. These studies have demonstrated that the organization and reinforcement of behaviors necessary to acquire sodium under deplete conditions require involvement of higher order fore-brain signaling processes.

The neurotransmitter dopamine and its release in forebrain target regions (e.g. nucleus accumbens [NAc]; dorsal striatum) were first proposed to be involved in reinforcement processes after the seminal studies of Roy Wise and colleagues [30,31]. However, the precise role of the neurotransmitter in motivated behavior is the subject of continued debate. Dopamine has been hypothesized to serve as a ‘teaching signal’ that can drive the formation of associations between environmental stimuli and positive outcomes [32, 33]. This seems to fit well with suggested cellular roles for dopamine in long-term potentiation and depression in regions like the NAc and striatum [34,35]. Mesolimbic dopamine is also important for enhancing the salience of, and directing behavior towards, reward-associated cues (incentive salience; [36]). Dopamine is also critical for more effortful responses required to obtain rewards [37]. While there are some aspects of these psychological constructs that are at odds with one another, the prevailing opinion is that dopamine plays a key role in assigning value to relevant stimuli and appropriately directing behavior towards those stimuli [38].

2. The generation of sodium appetite primes the mesolimbic system

Challenges to homeostasis prime dopamine circuits for responses to stimuli that satisfy the need state of the animal. Like the behavioral responses to homeostatic need, the dopamine system itself has been shown to be gated by physiological state. Metabolic state (e.g. hunger and satiety) and the hormonal proxies of metabolic state (e.g. ghrelin, insulin, leptin, GLP-1, amylin) bidirectionally regulate mesolimbic dopamine signaling. For example, food restriction increases the firing rate and burst firing of midbrain dopamine neurons [39]. In addition, in response to food, burst firing of midbrain dopamine neurons and striatal dopamine release are increased in food restricted animals [40–42]. Hormones that serve as proxies for hunger also increase dopamine neural activity [43], dopamine release [44] and the dopamine response to food [42] and food cues [45]. Conversely, satiety or hormonal manipulations inducing satiety decrease VTA neuron firing rate [46,47] and dopamine levels in the NAc [48–50].

Sodium appetite is also sufficient to induce changes in the mesolimbic system that could contribute to enhanced dopamine signaling when an animal encounters sodium or environmental cues that predict access to sodium. For example, sodium depletion alone decreases the rate of dopamine reuptake by the dopamine transporter (DAT; [51,52]). The hormone aldosterone, a mineralocorticoid, is critical for the expression of a sodium appetite [6]. Administration of aldosterone to NAc tissue, taken from rats in positive sodium balance (e.g. sodium replete), is sufficient to recapitulate the ability of sodium depletion to decrease the rate of dopamine reuptake [51]. A decrease in DAT binding was also observed in sodium replete rats treated with the mineralocorticoid deoxycorticosterone acetate (DOCA) [53]. Reduction in DAT number or function would result in increased extracellular dopamine exposure time and diffusion upon release [54,55]. In turn, extracellular dopamine would be increased over longer periods of time; an effect that has been associated with generating motivation and the vigor of goal-directed behavior [56]. Systemic delivery of mineralocorticoids alone is sufficient to increase phosphorylated tyrosine hydroxylase, suggesting that the hormonal response to sodium deprivation increases dopamine production and possibly signaling [57]. It is important to note that sodium depletion causes additional changes within the mesolimbic system such as the regulation of NAc neuropeptide production [58]. Together, these data indicate that sodium depletion and the hormones released in response to sodium deficit act either indirectly or directly on the mesolimbic system to modulate signaling with the potential for heightened dopamine signaling being a key feature.

3. The taste of sodium differentially drives mesolimbic activity based on physiological state

The sham drinking paradigm was developed to study ingestion in the absence of post-ingestive feedback signaling. Here, appetitive and consummatory behaviors directed at the taste of a stimulus can be isolated and carefully studied. Shamfed rats reduce consumption of palatable liquid sucrose following dopamine receptor antagonism [59]. We found that similar manipulations of the mesolimbic system reduce sham drinking of sodium solutions in sodium deplete rats [60]. This study, together with one showing a reduction in sodium

appetite in sham drinking rats by interference with taste transduction mechanisms (e.g. peripheral taste nerve transection; [61]), suggests that the taste of the sodium ion differentially drives dopamine signaling based on physiological state. Brief access to hypertonic sodium following sodium depletion is associated with an increase in the ratio of dopamine metabolites relative to dopamine [62] - indirect evidence of dopamine signaling and support of this hypothesis.

Recent work in our lab lends direct support for this hypothesis. We used fast-scan cyclic voltammetry to sample dopamine concentration changes in the NAc in 'real-time' (10 samples/s; [63]). Periodic intra-oral infusions of hypertonic NaCl were made in both sodium replete and deplete rats. Thus, dopamine measurements were commensurate with the sensory experience of ingestion. On individual trials, intra-oral NaCl evoked a high concentration increase in NAc dopamine, within 100 s of milliseconds of infusion onset, but only in sodium deplete rats [27; see also Fig. 1]. Consistent with the idea that state-dependent dopamine signaling is driven by the taste of sodium, we found that lingual blockade of amiloride-sensitive sodium channels eliminated the NaCl-evoked NAc phasic dopamine response in deplete rats [27].

Similar to dopamine release patterns, the responses of NAc output neurons (medium spiny neurons [MSNs]) to the taste of NaCl are modulated by sodium appetite. Electrophysiological recordings of MSN activity during intra-oral infusions show that appetitive stimuli (e.g. sucrose, saccharin) evoke decreases in the firing rate of the majority of taste-responsive neurons [64,65]. Aversive stimuli (e.g. quinine, sucrose after devaluation with lithium chloride in a conditioned taste aversion paradigm), on the other hand, evoke the opposite pattern – increases in the firing rate of the majority of taste-responsive neurons [64,66]. Interestingly, hypertonic NaCl evokes an aversive-like pattern of NAc activity in replete rats. However, after sodium depletion, the same solution evokes an appetitive-like pattern [67]. It remains unclear the degree to which differential dopamine signaling to NaCl in replete versus deplete conditions accounts for the different patterns of NAc neural activity. Since the NAc receives input from other sodium-appetite associated regions of the brain (e.g. the amygdala, [8,68–70]), it is possible that multiple mechanisms are responsible for differential NAc activity evoked by the taste of sodium in replete versus deplete rats. Still, state-dependent phasic dopamine release in the NAc likely contributes to the strong motivational drive to seek out sodium and reinforces consumption upon encountering a sodium source as detected by the gustatory system.

4. Potential mechanisms

Sodium balance gates the ability of the taste of sodium to drive dopamine release and appetitive encoding by NAc neurons. Multiple mechanisms are likely permissive and essential for the differential mesolimbic responses seen in replete and deplete rats. First, gustatory signals evoked by the sodium ion in the intra-oral cavity are altered by sodium depletion. NaCl responses of the chorda tympani nerve, a branch of the seventh cranial nerve that carries gustatory information from taste buds to the brainstem [71,72], and second order taste neurons in the nucleus of the solitary tract (NTS) [73] are modulated by sodium depletion [74]. Thus, drive from the gustatory system is different when sodium is tasted in a

deplete versus replete state. Second, as detailed above, sodium depletion and mineralocorticoids that are increased in response to depletion can act directly on the mesolimbic system to alter responsivity [51, 53,75]. Third, it is possible that sodium depletion increases NAc dopamine neurotransmission by increasing the excitability of dopamine neuron cell bodies in the ventral tegmental area (VTA) through afferent pathways. While empirical evidence has yet to emerge in support of this third possibility, the VTA does receive direct and indirect input from numerous sodium appetite regulatory centers of the brain [76].

The need for sodium is sensed by a population of neurons in the NTS. These neurons are activated by sodium depletion [77] and are sensitive to aldosterone and other indicators of sodium deficiency [78]. These hindbrain “HSD2” neurons, named for their expression of the glucocorticoid-inactivating enzyme 11- β -hydroxysteroid dehydrogenase type 2, are well positioned to integrate hormonal and neural signals communicating body fluid homeostasis. HSD2 neurons are located around a blood-brain barrier-deficient zone of the NTS allowing for access to hormonal signals relaying sodium need (i.e. aldosterone) [79]. These same neurons also detect the ingestion of sodium through direct sensory input from the gut via the vagus nerve [80] or indirectly through projections from the area postrema (AP), a circumventricular organ that monitors changes in plasma hormones [81]. While direct projections from HSD2 neurons to the VTA have not yet been shown, it is plausible that HSD2 neurons monitor body fluid homeostasis and tune mesolimbic dopamine signaling through several multisynaptic connections to the VTA.

Both NTS HSD2 [77] and AP neurons [82] project to two visceral relay centers: the prelocus coeruleus nucleus (pre-LC) and the inner division of the external lateral parabrachial subnucleus (PBel-inner). All pre-LC and PBel-inner neurons that become c-fos activated with sodium depletion constitutively express a transcription factor called Forkhead box protein 2 (FoxP2) [83]. These FoxP2 cells project directly to the VTA as well as various other midbrain and forebrain sites which potentially influence mesolimbic circuitry [76]. It is likely that the VTA uses these inputs to evaluate a sodium taste stimulus based on physiological state and responds with the generation of an appropriate dopamine response (Fig. 2). Interestingly, lesions of the parabrachial nucleus eliminate sodium appetite [84,85], pointing to this structure as a logical site to explore for passing critical taste/state information to the VTA. Future studies will be needed to determine the essential gating mechanisms by which physiological state alters the mesolimbic response to the taste of hypertonic sodium solutions.

5. What is the role of the mesolimbic system in sodium appetite?

While dopamine antagonists suppress the sham drinking of NaCl in sodium deplete rats, neither systemic [60] nor intra-NAc [58] dopamine antagonism has an effect on the expression of sodium appetite in rats with intact post-ingestive feedback. These results are supported by a handful of studies which demonstrate that dopamine is not essential for sodium appetite [36,86,87]. Instead, dopamine may serve to facilitate ingestive behavior through its neuromodulatory actions on MSNs. For example, dopamine binding to the D2 receptor is thought to inhibit the activity of D2-expressing MSNs [35]. In turn, NAc

inhibitory responses to taste are correlated with licking and appetitive behavior ([64,67,88] but also see [70]).

While dopamine release may facilitate NAc encoding that promotes consumption, it may also play a role in plastic changes to NAc circuits. NAc dopamine has long been thought to play a role in reinforcement, with phasic dopamine responses serving as a teaching signal [32,33]. The phasic dopamine responses evoked by hypertonic NaCl under sodium deplete conditions [27, Fig. 1] are similar to those observed in response to a sucrose reward in hungry rats [89]. Similarly to phasic dopamine responses evoked by other rewards, phasic dopamine comes to be evoked by cues predictive of hypertonic NaCl but only when rats are trained and tested in a sodium deplete state [27]. This learned response can serve to incentivize approach and consumption under the right physiological and environmental conditions [26].

Randal Sakai found that sodium intake is enhanced with multiple sodium depletions [90]. This sensitization of sodium appetite parallels the increased behavioral response to psychostimulants after repeated injections. We found that multiple sodium depletion episodes induce morphological changes [75] that are similar to those observed following sensitization to psychomotor stimulants (e.g. cocaine, amphetamine; [91,92]). Sodium depletion also cross-sensitizes responses to psychostimulants [75,93] – suggesting overlapping physiological underpinnings of sodium- and drug-directed behaviors under particular conditions. Interestingly, it has been suggested that after multiple depletion episodes, the consumption of sodium under deplete conditions no longer causes the release of dopamine, as dopamine metabolite/dopamine ratios do not increase to sodium after multiple depletions [62]. These results suggest that after the initial sodium deprivation, dopamine signaling may play less of a role in the behavioral and neuroendocrine responses to deprivation. It is therefore possible that the initial dopamine-dependent reinforcement of the taste of NaCl under deplete conditions is sufficient to induce plasticity within the NAc that underlies subsequent seeking and consumption upon reencountering NaCl in a deficient state.

Randall's work is among seminal studies which identify the hormonal response to sodium deficiency and its actions on central circuits which drive compensatory behavior. Collectively, this work presents a relatively well-described series of biological events to explain how motivated behavior arises from homeostatic challenge. The involvement of the mesolimbic system in body fluid homeostasis is certain, although the nature of its involvement remains unclear. The same is true in the case of energy balance, where the mesolimbic system is modulated by the same peptides and hormones which regulate food intake through actions on hypothalamic and hindbrain sites [94–99]. However, compared to food deprivation, the physiological responses to sodium depletion are more thoroughly characterized. In using sodium appetite to understand the role of the mesolimbic system, general insight into the central responses to homeostatic challenge can be determined. In so doing, future work can speak to a therapeutic intervention at the level of the mesolimbic system for over-consumption of salt, sugar and calories that might protect against cardiovascular disease and obesity.

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HIGHLIGHTS

- Sodium appetite primes neural circuits critical for motivated behavior
- Taste and state are integrated to differentially drive mesolimbic activity.
- Dopamine signaling is likely tuned by multisynaptic hindbrain to VTA circuits.

Fig. 1.

Intra-oral infusion of 0.45 M NaCl evokes increases in NAc core dopamine release in only sodium deplete animals. (*Top*) Single-trial colorplots depict changes in current (color) as a function of applied electrical potential [E_{app} (V); y-axis] and time (s; x-axis). Dopamine [identified by its oxidation peak (~ 0.6 V, green feature)] was evoked during the 4-s intra-oral infusion period (beginning at 0-s and indicated by the horizontal bar below) in sodium deplete (right) but not sodium replete (left) rats. (*Bottom*) Dopamine concentration changes in response to 0.45 M NaCl in sodium replete (blue) and sodium deplete (orange) rats. Concentration changes were extracted from the colorplots above. Current from the oxidation of dopamine was converted to concentration using post-recording calibration of the electrodes used during data collection.

Fig. 2.

Theoretical circuit-level diagram depicting VTA inputs that drive dopamine responses in the NAc under sodium replete and deplete conditions. (Left) Under sodium replete conditions, the taste of NaCl fails to evoke an increase in NAc dopamine (blue concentration trace). The NTS represents a hypothetical path for gustatory information to influence NAc dopamine signaling. Although direct projections from the NTS to the VTA have been reported, it remains unclear if these inputs convey gustatory information. Blue arrows denote a potential route for gustatory information from the oral cavity to influence the VTA. (Right) Following sodium depletion, taste input (blue arrows) converges on the VTA with hormonal and visceral input (orange arrows) to drive increases in NAc dopamine to the taste of NaCl (orange concentration trace). Hormonal and visceral input is transmitted to the NTS through both circulation and vagal input. The NTS carries signals communicating sodium need to the pre-LC and PBel, both of which send direct projections to the VTA (orange arrows). In addition, circulating hormones may act directly on the VTA or NAc (orange circles) to gate dopamine release in response to NaCl.