Pflugers Arch - Eur J Physiol (2015) 467:445–456
DOI 10.1007/s00424-014-1676-y

INVITED REVIEW

The biopsychology of salt hunger and sodium deficiency

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Received: 1 October 2014 / Revised: 9 December 2014 / Accepted: 15 December 2014 / Published online: 10 January 2015

Abstract Sodium is a necessary dietary macromineral that tended to be sparsely distributed in mankind's environment in the past. Evolutionary selection pressure shaped physiological mechanisms including hormonal systems and neural circuits that serve to promote sodium ingestion. Sodium deficiency triggers the activation of these hormonal systems and neural circuits to engage motivational processes that elicit a craving for salty substances and a state of reward when salty foods are consumed. Sodium deficiency also appears to be associated with aversive psychological states including anhedonia, impaired cognition, and fatigue. Under certain circumstances the psychological processes that promote salt intake can become powerful enough to cause "salt gluttony," or salt intake far in excess of physiological need. The present review discusses three aspects of the biopsychology of salt hunger and sodium deficiency: (1) the psychological processes that promote salt intake during sodium deficiency, (2) the effects of sodium deficiency on mood and cognition, and (3) the sensitization of sodium appetite as a possible cause of salt gluttony.

Keywords Homeostasis · Motivation and reward · Salt appetite · Mood · Hypertension

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Introduction

Animals maintain body fluid homeostasis by regulating the distribution and concentration of water and sodium. Animals face different challenges to body water and sodium content depending on their environmental niche [113]. For example, the distribution and types of ions present in the intracellular and extracellular spaces of aquatic animals are dependent on whether they live in fresh or salt water environments. Aquatic animals are characterized as either osmoconformers that regulate extracellular fluids to match the osmolality of their environment or osmoregulators that regulate osmolality within a strict range (~300 mOsm). By the nature of their environment, terrestrial animals are osmoregulators that continually lose body water and sodium through normal physiological processes and environmental conditions. In order to replenish lost water and sodium, terrestrial animals must engage in behaviors associated with *thirst* and *sodium appetite*, or the seeking and ingestion of water and salty substances, respectively. Terrestrial animals exhibit thirst fairly often because significant amounts of water are lost from the body due to respiration, transpiration, and through the formation of urine. Although sodium is excreted along with water through normal physiological processes including urination, defecation, and sweating, body sodium must be taxed to a fairly large extent before a sodium appetite can be evoked. Thus, sodium appetite results from less-common circumstances that cause a considerable deficit in body sodium including pregnancy, vomiting, sweating, hemorrhage, diarrhea, and long-term maintenance on a sodium-deficient diet [1, 13, 62, 79, 88, 98].

Sodium-deficient diets provided the selection pressure that shaped neural and hormonal systems which act to promote sodium appetite in herbivores and omnivores [32, 43, 70]. Carnivores ingest sufficient amounts of sodium from viscera and muscle tissue of their prey, and when tested under sodium-deficient conditions, carnivores either fail to exhibit

sodium appetite or exhibit a weak sodium appetite [124]. In contrast, herbivores subsist off plant diets that tend to be very low in sodium. As such, herbivores exhibit a robust sodium appetite under sodium-deplete conditions [31]. Perhaps, one of the best-known examples of herbivores' robust sodium appetite is the ingestion of concentrated sodium in the form of salt blocks by cattle and deer. Omnivores also exhibit sodium appetite under sodium-deplete conditions [3, 114, 127]. Early humans may have been particularly prone to sodium depletion as they primarily lived in arid environments that were bereft of sodium and a majority of their diet consisted of plant matter [32]. These environmental conditions provided the selection pressure for the development of a set of physiological mechanisms that would help maintain and replenish sodium stores in humans.

Salt appetite

Wilkins and Richter presented a striking example of how sodium deficiency drives the powerful motivated state of sodium appetite [132]. Their case study discussed a child who was incapable of synthesizing the steroid hormone aldosterone causing him to continually excrete sodium. As a result, the child exhibited a near-continuous salt appetite. The child also exhibited a robust thirst that may have been caused by the large amounts of salt he was ingesting. His thirst and salt appetite were so powerful that they caused him to engage in aberrant psychological responses in order to obtain water and salt. For example, he had a desire to drink ocean and river water. His ongoing salt appetite caused him to only eat foods that contained high concentrations of salt and even led to him ingesting salt directly from the salt shaker. His motivation to obtain salt was so dominant that one of the first words he learned to speak was salt.

The child in Wilkins and Richter's case study had experienced what is known as *need-induced* sodium intake. Need-induced sodium intake is operationally defined as the robust salt intake that occurs when an animal is in a sodium-deficient state. This type of sodium intake is often referred to as sodium appetite. However, it is worth noting here that sodium appetite can also be stimulated through manipulations that mimic the physiological precursors of sodium appetite without actually inducing a sodium deficit such as administration of aldosterone and angiotensin II (Ang II; [15, 34, 44, 121]). Animals that are sodium replete also consume salt ad libitum, and this type of salt ingestion is known as *need-free* sodium intake [123]. Currently, the biological mechanisms that mediate need-induced salt intake are better understood than those that determine need-free intake. However, need-free salt consumption is probably more relevant to the excess salt intake that is observed in some humans [27, 36, 99]. A discussion of need-free salt intake is presented in the "Salt gluttony and the sensitization of sodium appetite" section.

A majority of our understanding of the physiological and neurobiological mechanisms that mediate sodium appetite is derived from studies examining laboratory rats. In fact, Curt Richter was the first to provide experimental evidence demonstrating the existence of sodium appetite using adrenalectomized rats [114]. Sodium appetite is commonly assessed in laboratory rats by measuring the ingestion of hypertonic saline solutions that generally range between 1.5 and 9.0 %*w/v* NaCl. These solutions elicit a set of aversive behaviors when they are involuntarily tasted by sodium-replete rats due to the high salt concentration [6, 51]. Therefore, under normal conditions, rats ingest relatively low amounts of hypertonic saline solutions. However, when rats become sodium deficient, processes in the central nervous system are engaged that promote the ingestion of salty substances [5, 6, 115].

Sodium depletion evokes processes in the central nervous system that induce the motivated state of sodium appetite. Sodium appetite is associated with central nervous system mechanisms that alter the appraisal of salty substances. One such process is referred to as the *hedonic shift* that occurs during sodium depletion [6]. The hedonic shift is characterized by a change in the hedonic appraisal and incentive value of salty substances. In other words, during sodium depletion, animals begin to appraise salty substances as more palatable (i.e., the hedonic quality of sodium becomes increasingly positive; [6, 115]) and animals begin to seek out and ingest salty substances (i.e., the incentive value of salty substances is increased [19, 115]). Perhaps, the most striking demonstration of the hedonic shift associated with sodium appetite has come from the work of Kent Berridge and colleagues. They have been assessing sodium appetite by measuring the intake of Dead Sea concentrations of hypertonic saline (9 % NaCl; [115]). When sodium-replete rats taste this very high salt concentration, they exhibit a pattern of species-specific orofacial and forelimb behaviors that are indicative of aversion/disgust. Furthermore, when placed in a cage with a lever that can be pressed to produce intra-oral delivery of Dead Sea hypertonic saline, rats will learn to associate the lever with the aversive flavor of hypertonic saline and as such they will avoid and bury it [115]. However, when rats are made sodium deficient, they perform approach behaviors towards the lever, lick the lever, and press it to obtain sodium. Once they taste the concentrated saline, rats will engage in a pattern of species-specific behavioral responses that indicate that the taste of salt is rewarding [51]. The same set of responses is also emitted when rats drink sweet sucrose solutions. Therefore, sodium depletion is capable of shifting the hedonic value of salt from a negative (aversive) to a positive (rewarding) stimulus [5, 6]. Furthermore, it appears that this hedonic shift for salt occurs before sodium-depleted rats have even had the opportunity to voluntarily ingest salt [115]. The first time rats

become sodium depleted, they will avidly lever-press to obtain Dead Sea hypertonic saline despite the fact that all their prior experience with this solution had been negative.

Sodium depletion also appears to reduce the incentive value [52, 88, 90, 96, 97] and possibly the hedonic impact of salt-lacking foodstuffs [3, 88, 132]. Michael McKinley recently provided strong experimental evidence for this idea in a study that examined rats' preferences for salted and unsalted biscuits in sodium-replete and sodium-deficient states [90]. He found that sodium-replete rats preferred unsalted biscuits over salted biscuits. However, when rats were made sodium deficient, they expressed a preference shift that was marked by an increase in salted biscuit intake and a decrease in unsalted biscuit intake. Importantly, McKinley also showed that antagonism of Ang II receptors prevented the increase in salted biscuit intake caused by sodium depletion, but Ang II antagonism had no effect on the reduced intake of unsalted biscuits. One important conclusion that can be drawn from this study is that salt appetite is associated with two processes that appear to have different physiological underpinnings. One process promotes salted food intake and the second suppresses unsalted food consumption. An experiment from our laboratory that examined whether sodium depletion would alter the intake of salted and unsalted potato chips yielded similar results (Fig. 1). We found that rats generally preferred unsalted chips over salted chips, but sodium depletion caused a clear preference shift towards salted chips. Depleted rats actually reduced their intake of unsalted potato chips and increased their intake of salted potato chips. The data from animal experiments are consistent with experiments showing that sodium deficiency changes how humans evaluate foods of varying salt content. Sodium-depleted humans rate salted foods as *more* appealing and unsalted foods as *less* appealing [3]. This may be captured in the statement from one sodium-depleted volunteer who reported that "[unsalted] food was tasteless, even highly flavored food. Chewing fried onions, for example, evoked only a sensation of greasy sweetness which was extremely nauseating" [88]. Similarly, the child that was discussed in Wilkins and Richter's case study had refused to eat sweet foods [132], possibly because his hunger for salt had diminished the common craving children have for sweets.

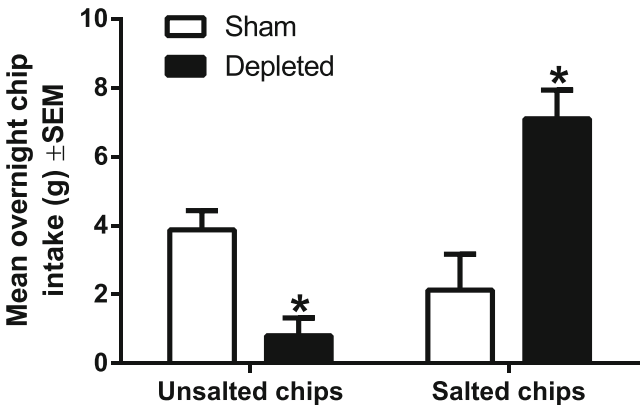

Fig. 1 The effect of sodium depletion on the preference for unsalted and salted potato chips. Rats were depleted via treatment with the diuretic and natriuretic furosemide. Twenty-one hours after furosemide treatment, rats were allowed access to crushed unsalted and salted chips. Overnight intakes were recorded. Sodium-depleted rats exhibited a decrease in unsalted chip intake and an increase in salted chip intake ($p<0.05$ vs. sham depleted animals)

The shift in preference for salted and unsalted foods that occurs during sodium depletion most likely operates to promote goal-directed behavior towards salty substances. It appears that salt appetite is associated with a form of reward reevaluation where salty substances are wanted and liked more than salt-lacking rewards [3, 6, 90]. This may ultimately serve to decrease the likelihood that an animal will pursue salt-lacking rewards while increasing the likelihood that animals will seek out and ingest salty substances. If this is true, then, central nervous system mechanisms that promote the reevaluation of rewards based upon their salt content would be beneficial. Severe loss of sodium is life threatening, and it is imperative that sodium-deficient animals find and consume salt. Seeking out rewards that lack sodium would only deter them from replenishing body sodium content, and this could potentially jeopardize survival.

The physiology and neurobiology of sodium appetite

Sodium appetite is promoted through the coordinated activity of physiological mechanisms in the central nervous system and periphery [67]. Sodium depletion results in a state of dehydration of the extracellular fluid compartment that is associated with reduced total body fluid. This decrease in total fluid volume has marked effects on cardiovascular function, and as a result, physiological responses are engaged to protect and restore fluid volume. Blood volume is primarily monitored by high- and low-pressure baroreceptors located in organs that regulate cardiovascular function including the kidneys, heart, and vasculature [12, 29, 67]. Baroreceptors detect the decrease in blood volume caused by extracellular dehydration and trigger hormonal and sympathetic responses to promote water and sodium retention, redistribution of blood flow to preserve adequate organ perfusion, and the behavioral responses of thirst and sodium appetite [109]. These physiological and behavioral responses are largely controlled by two renin-angiotensin-aldosterone-systems (RAASs); one RAAS is an endocrine system in the periphery, and the second is a neurotransmitter/neuromodulator system located in the brain [34, 35, 46, 121].

During a state of extracellular dehydration, the peripheral RAAS is engaged which begins with the release of renin from the kidneys into circulation. Renin circulates in the plasma where it cleaves constitutively present angiotensinogen into

angiotensin I. Angiotensin I is biologically inert and serves as an intermediate peptide that becomes converted by angiotensin-converting enzyme (primarily located in the lungs and vasculature) into the octapeptide Ang II. In many ways, Ang II is the centerpiece of correcting body fluid homeostasis. Ang II coordinates many of the physiological and behavioral responses necessary to defend and restore body fluids [15, 46, 109, 112]. This peptide acts directly on the vasculature to promote vasoconstriction and also triggers the release of two hormones critical for regulating mineralo-fluid balance—vasopressin and aldosterone [16, 71]. Vasopressin is synthesized in the magnocellular neurons of the hypothalamus [130] and secreted from the posterior pituitary into the circulation to promote vasoconstriction and water retention by the kidneys. Aldosterone is a steroid hormone released from the adrenal cortex that promotes renal sodium retention and sodium appetite. Ang II acts in the brain to mobilize thirst and synergizes with aldosterone to initiate sodium appetite [34, 44]. In addition to the peripheral RAAS, the synthetic enzymes and precursors necessary for Ang II and aldosterone synthesis are present in the central nervous system [40, 47, 49]. Therefore, Ang II acts as a neurotransmitter [40] and aldosterone acts as a neuromodulator [49, 50], and they most likely serve as synaptic and paracrine signals in the brain to raise blood pressure and promote thirst and salt appetite [34, 44, 65].

The neural circuitry regulating fluid balance involves the coordination between hindbrain and forebrain nuclei that essentially serve the purpose of sensing changes in mineralo-fluid balance and blood volume [64, 67]. In the hindbrain, the nucleus of the solitary tract (NST) and adjacent area postrema (AP) play a critical role in monitoring body fluid homeostasis [67, 93]. These areas are sensitive to circulating Ang II and aldosterone, osmotic concentration, and changes in blood pressure. The NST projects to the lateral parabrachial nucleus (LPBN), and together, these structures exert tonic inhibition on sodium appetite [23, 92]. It is likely that a confluence of internal signals, including a drop in blood pressure or volume and an increase in circulating and central Ang II and aldosterone, alter activity in the NST and AP which results in a disinhibition of sodium appetite [67].

In the forebrain, an ensemble of brain nuclei located along a region of the brain known as the lamina terminalis (LT) contribute to the regulation of mineralo-fluid balance [42, 65, 67, 91]. The nuclei located along the LT include the subfornical organ (SFO), median preoptic area (MnPO), and organum vasculosum of the lamina terminalis (OVLT). The SFO and OVLT deserve significant attention because these structures lack a blood-brain barrier [66]. This grants them the capability of monitoring the osmotic status of circulating plasma as well as hormonal Ang II and aldosterone. Osmotic concentration and circulating levels of Ang II and aldosterone are detected by the SFO and OVLT, and this information is integrated in the central nervous system to initiate thirst and sodium appetite [91]. The MnPO appears to act as a relay that receives information from both the SFO and the OVLT [81].

Although structures along the LT and hindbrain detect when the body is in a state of a sodium deficit, these sensory areas must work in tandem with neural circuitry that promotes motivated behavior in order for an animal to engage in thirst and salt appetite. In other words, sodium-depleted animals need to become active and begin navigating the environment to find the nearest source of salt. Brain areas that mediate appetitive motivated behaviors essentially energize behavior (i.e., promote a state of physiological and psychological arousal) and direct behavior towards a goal object in the environment [8, 9]. An important neural pathway that appears to mediate all appetitive motivated behaviors is the dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), referred to as the mesolimbic dopamine system [72, 94]. Increased activity in the NAc is correlated with the presence of a sodium appetite [80, 101, 117].

Sodium depletion alters how the nervous system, including structures within the mesolimbic dopamine system, processes the taste of salt [21, 61, 82, 128]. Sodium deficiency reduces gustatory nerve responses to salt [21, 22]. Neurons within the NST, which receives afferent information from the gustatory nerves, also exhibit altered firing patterns to the taste of salt during deficiency [61]. Similar to the changes in firing observed in the gustatory nerves, the salt-responsive neurons in the NST exhibit reduced firing during deficiency. Interestingly, neurons that respond to sweet tastes such as sucrose begin to fire in response to salty tastes in the depleted animal [61]. Areas in the forebrain that code the motivational and rewarding value of stimuli exhibit a different profile of responses to the taste of salt during sodium deficiency [82, 128]. Neurons in the NAc appear to be involved in evaluating the motivational valence of stimuli [116, 119]. In other words, the NAc plays a role in determining whether stimuli in the environment should be approached or avoided [39]. An inverse relationship exists between neuron firing rate in the NAc and the rewarding properties of taste stimuli [116]. Specifically, neurons in the NAc exhibit an increase in activity in response to aversive tastes such as quinine. In contrast, palatable tastes like sweet sucrose solutions reduce firing rate in the NAc. The inhibition of NAc neurons that occurs in response to palatable tastes appears to be caused by the release of the neurotransmitter dopamine from neurons originating in the VTA projecting to the NAc [119]. With respect to sodium appetite, NAc neurons exhibit either an increase or decrease in firing rate in response to the taste of hypertonic saline solutions depending on the homeostatic state [82]. Rats that are in sodium balance show increased firing of NAc neurons to the taste of hypertonic saline solutions. However, sodium-deficient rats exhibit a reduced firing rate [6, 82]. In other words, in sodium-replete rats, the NAc processes salty tastes similar to how it processes the taste of bitter quinine solutions [82, 116]. Sodium

deficiency changes how the NAc processes salty tastes such that firing patterns are consistent with the response to sweet sucrose solutions [82, 116]. This indicates that the dynamic evaluation of the rewarding or aversive quality of salty tastes is associated with a change in the activity of NAc neurons. Interestingly, sodium depletion also alters how neurons respond to salty tastes in the posterior ventral pallidum (VP), a brain region that has been implicated in generating reward [126]. Neurons in the VP are normally unresponsive to the taste of hypertonic saline solutions [128]. However, during sodium deficiency, neurons in the VP exhibit increased firing in response to the taste of hypertonic saline solutions. These experiments suggest that the experience of sodium depletion can produce significant changes in how brain areas that code reward and the motivational valence of environmental stimuli process salty tastes. It is likely that the coding of salty tastes in the NAc and VP is influenced by activity in structures along the LT and hindbrain that are involved in sensing deficits in body fluid homeostasis. The changes in how the NST, NAc, and VP process salty tastes may be necessary for the hedonic shift that occurs during sodium depletion.

Negative effects of sodium depletion on psychological functioning

In 1935, Lieutenant-Colonel McEwen published a report in the Lancet while he was stationed in Punjab, India [89]. He noted that his colleagues and he were having a difficult time functioning in the hot climate of India. He reported that soldiers were experiencing "lassitude, headache, sleeplessness, and an inability to concentrate." McEwen had proposed that these ailments were caused by the salt loss associated with excessive sweating. He also noted that the local residents placed a great importance on eating high salt diets, possibly because this protected them from sodium deficiency. McEwen found that the consumption of saline solutions and the addition of relatively large quantities of salt to the diet ameliorated many of the negative ailments caused by excess sweating. Similarly, human participants depleted of sodium in an experimental setting reported symptoms of lassitude and muscle cramps [88]. A case study of a miner who had experienced excessive sodium loss also reported that he suffered from severe cramping in addition to fatigue [98]. These reports suggest that sodium depletion is associated with the psychological impairments of cognitive dysfunction and fatigue. Symptoms that appear to be associated with volume depletion are identical to those present in patients with chronic fatigue syndrome, which is characterized by "weakness, muscle pain, impaired memory and/or mental concentration, and insomnia" [18, 95]. Interestingly, one study found that patients who had significantly reduced their dietary sodium intake also exhibited signs and symptoms similar to those of chronic fatigue syndrome [10]. When treated with a therapy that consisted of increased salt consumption along with administration of drugs that raise blood pressure, most of the patients either improved or recovered completely. A separate study that measured the correlation between the extent of extracellular dehydration and psychological function in the elderly found that extracellular dehydration was directly correlated with impaired cognitive function (aka delirium; [125]). Together, these studies support the idea that sodium depletion can cause psychological impairments including fatigue and cognitive dysfunction.

Recent studies have also provided support for the possibility that sodium depletion induces anhedonia [52, 95–97]. Anhedonia is defined as a reduced or absent feeling of pleasure from activities or stimuli that normally evoke pleasure, and it is one of the major criteria for the diagnosis of major depressive disorder. Experiments in laboratory rats have provided the strongest evidence supporting sodium depletion-induced anhedonia. Although laboratory animals cannot report that they are anhedonic, changes in behavior can be indicative of anhedonia [17, 105]. In general, treatments or experiences that induce anhedonia in laboratory animals cause them to lose interest in engaging in rewarding activities [107]. For example, measuring the intake of palatable sucrose solutions can provide insight into whether a rat is exhibiting anhedonia. Rats find sucrose solutions rewarding and will drink a significant quantity of these solutions without any preceding conditions that stimulate hunger (e.g., food deprivation). However, if rats are subjected to treatments that induce anhedonia, such as exposure to various stressors, they will exhibit reduced sucrose intake [107]. It is also interesting to note that the exposure to stressors can reduce salt intake as well [77]. It has been reasoned that the reduction in sucrose consumption is essentially caused by the reduced pleasure rats get from ingesting these solutions.

A second method to test anhedonia in laboratory animals utilizes intracranial self-stimulation (ICSS; [17]). ICSS was a technique originally developed by Drs. James Olds and Peter Milner [106] who had used it to identify regions of the brain that mediate reward. It was reasoned that if rats were willing to learn a novel behavior, such as depressing a lever, in order to obtain electrical stimulation of a brain region, then, stimulation of that region is rewarding. Olds and Milner discovered that stimulation of numerous brain regions was capable of supporting avid lever-pressing by rats. The rewarding value of ICSS can be manipulated by altering the frequency and amplitude parameters of electrical stimulation. Increasing the extent of electrical stimulation by raising the frequency or amplitude produces a greater level of reward, and this is reflected in behavior. When stimulation is increased, rats will exhibit a greater rate of lever-pressing. Treatments that induce anhedonia, however, result in a reduction in lever-pressing for

ICSS, presumably because the stimulation is less rewarding [17, 96]. Therefore, ICSS can be used to probe whether certain treatments are capable of inducing a state of anhedonia.

The sucrose intake and ICSS models of anhedonia have provided support to the idea that sodium depletion can induce anhedonia. Sodium deficiency reduces palatable sucrose consumption in rats [52, 77]. Similarly, sodium depletion also reduces lever-pressing for ICSS [96]. When sodium-depleted rats are allowed to consume saline solutions and body sodium content is restored, they no longer exhibit changes in behavior that are indicative of anhedonia [96]. Interestingly, the anhedonia that accompanies sodium depletion appears to be caused by a craving for salt rather than sodium deficiency [95, 97]. This is supported by the observation that manipulations which induce sodium appetite without causing sodium deficiency also reduce lever-pressing for ICSS. Specifically, administration of deoxycorticosterone acetate (DOCA), which is a precursor to aldosterone, induces a sodium appetite that is accompanied by sodium retention. DOCA-treated rats exhibit behaviors indicative of anhedonia such as reduced lever-pressing for ICSS [97]. When DOCA-treated rats are allowed access to hypertonic saline solutions, ICSS responding returns to normal. These experiments indicate that the anhedonia associated with sodium depletion is not caused by a deficit in body sodium or hypotension caused by volume depletion. Sodium depletion-induced anhedonia appears to be, in essence, caused by the psychological craving for salt rather than the effects of sodium depletion on physiological functioning [95–97]. Although a link between anhedonia and sodium deficiency in humans has not been explicitly tested, at least one study hints that sodium deficiency may cause anhedonia in humans. This study found a significant association between hypotension, which can be caused by volume depletion, and reduced positive affect in the elderly [68].

One approach to understanding the anhedonia that appears to be exhibited during sodium depletion is conceptualizing it as a by-product of the goal direction that drives animals to ingest salt when they are experiencing a sodium appetite (see "Salt appetite" section). Anhedonia indicates that the hedonic impact of normal rewards is diminished; however, it is clear that salt is rewarding to the sodium-deficient animal. Therefore, it is likely that the behavioral changes that are indicative of sodium depletion-induced anhedonia reflect a central nervous system process that reduces the rewarding value of salt-lacking rewards in order to define which rewards should be pursued in the environment. This would serve the purpose of filtering the number of potential rewards so that an animal will primarily pursue those that contain salt. As mentioned previously, depleted rats will choose foods enriched in salt over unsalted foods (Fig. 1; [90]). Furthermore, sodium-depleted rats are more likely to drink hypertonic saline rather than lever-press for ICSS [20].

Salt gluttony and the sensitization of sodium appetite

The average sodium intake in most Westernized societies is far in excess of that which is required for normal physiological function [14, 27]. Excess salt intake, also known as salt gluttony [124], can have detrimental effects on health [86]. Many reports have indicated that excess salt intake contributes to cardiovascular disease and mortality, especially in salt sensitive individuals [14, 26–28, 131]. Recently, the observation that high salt intake can contribute to autoimmune disease has also garnered significant attention [73]. Therefore, it is likely that reducing salt intake, especially in salt sensitive individuals, would have beneficial effects on public health. For example, one projection predicts that a nationwide reduction of salt intake in the USA could save 92,000 lives per year and reduce health-care costs by US$10 to US$24 billion per year [7]. A recent study concluded that 1.65 million worldwide cardiovascular disease-related deaths in 2010 were attributable to high salt intake [99]. Therefore, understanding the factors that contribute to excess salt intake will have a beneficial impact on public health [36]. Several ideas have been proposed to explain excess salt intake (for review, see [78]). These ideas range from stress-induced salt intake [33, 55] to learned preferences for salty foods [133]. One potential determinant of salt gluttony that has been gaining increased experimental scrutiny is the sensitization of sodium appetite, or the seemingly lifelong increase in salt intake that occurs after sodium depletion [59, 122].

Sodium appetite sensitization was originally discovered by John Falk in 1965 [37]. Falk sodium depleted rats on two separate occasions and found that rats ingested more hypertonic saline on their second depletion. Since then, sodium appetite sensitization has been replicated by numerous laboratories using protocols that elicit sodium appetite either through sodium depletion [30, 37, 38, 111, 122, 123] or pharmacological means [15]. Perhaps, the most relevant aspect of the sensitization of sodium appetite is that it also produces a lifelong increase in daily (aka need-free) salt intake [36, 122, 123]. Sodium appetite sensitization appears to be a form of non-associative learning that is expressed through enhanced sodium intake [38, 45]. Sodium intake plateaus after one to three depletions, depending on the sodium depletion protocol employed [37, 45, 57, 111, 122, 123]. Furthermore, sodium appetite sensitization also potentiates the drive to obtain sodium that is exhibited during sodium deficiency [19].

Enhanced sodium appetite has been found to be present in humans who have experienced sodium depletion perinatally [25, 75]. Specifically, the children of mothers who were repeatedly sodium depleted during pregnancy exhibit greater salt intake in adulthood [25]. Similarly, infants that experienced repeated bouts of salt loss due to vomiting or diarrhea show an increase in salt intake during adolescence [75]. Currently, there is no available evidence that supports the idea that

sodium depletion during adulthood produces lifelong increases in need-free salt intake [76]. However, this may simply be due to the fact that virtually every adult human has experienced sodium deficiency during their lifetime and, as such, an adequate control group with no history of sodium depletion may not exist.

Neural plasticity and the sensitization of sodium appetite

The enhanced sodium ingestion associated with sodium appetite sensitization is not caused by an increase in circulating levels of angiotensin II or aldosterone, as neither of these hormones becomes elevated after repeated sodium depletions [123]. Therefore, one hypothesis is that sodium depletion alters central nervous system circuitry beyond the body-to-brain signaling role of circulating angiotensin II and aldosterone [59]. In other words, it is likely that sodium depletion induces neural plasticity in the central nervous system to drive elevated salt consumption [57]. Neural plasticity is essentially the process by which neurons change in structure or function in response to experience [48, 134]. Neural plasticity can be observed as long-term changes in neuron morphology, receptor expression, and neurotransmitter synthesis, among other changes. Many forms of plasticity require the activation of glutamatergic *N*-methyl-D-aspartate receptors (NMDA-Rs; [53, 69, 129]). The NMDA-R is a unique gated ionotropic receptor that only enters an open state when glutamate is bound to the receptor and the neuron upon which it is present is sufficiently depolarized. Therefore, the unique properties of the NMDA-R provide a physiological mechanism that allows for Hebbian learning [54], where the co-activation of neurons increases the strength of the connection between those neurons (put simply—neurons that fire together, wire together; [24]). Blockade of NMDA-Rs prior to sodium depletion with the non-competitive NMDA-R antagonist MK-801 prevents the development of sodium appetite sensitization [57].

It appears that two neural circuits undergo plasticity in response to sodium depletion: one neural circuit is located along the LT and regulates body fluid homeostasis, and the second is the mesolimbic dopamine system. Lesions of the SFO, which is a critical component of the sensory apparatus that aids in detecting deficits in body fluid homeostasis [66], prevent the increase in need-free intake that occurs after sodium depletion [120]. The SFO also appears to exhibit increased activity during sodium deficiency in sensitized rats [101]. Whether the other brain areas that monitor body fluid homeostasis such as the OVLT, MnPO, and NST are important for the sensitization of sodium appetite remains to be tested. Sodium depletion also induces neural plasticity in the mesolimbic dopamine system [101, 118]. The experience of repeated episodes of sodium depletion increases the dendritic length and arborization of NAc neurons [118]. Additionally, sensitized rats show increased activity of NAc neurons during sodium deficiency [101]. We have recently found that microinjection of the NMDA-R antagonist AP-5 into the VTA, the region that provides the dopaminergic innervation of the NAc, prevents the sensitization of sodium appetite [59]. One possibility is that neural plasticity occurs in the VTA after sodium depletion, and this plasticity is passed on to the NAc [87].

One approach to explaining the sensitization of sodium appetite is that the neural processes that are engaged to promote salt seeking and ingestion during sodium appetite (see "The physiology and neurobiology of sodium appetite" section) leave behind a memory trace that permanently elevates animals' salt intake. In other words, sodium depletion induces a change in activity across neural circuits, including the LT and the mesolimbic dopamine system, which drives sodium appetite [67, 80, 117]. However, the change in activity that occurs along the LT and mesolimbic dopamine system may not return to baseline levels after sodium depletion. It is possible that, through mechanisms involving NMDA-R-dependent neural plasticity [57], the memory of salty tastes becoming increasingly desired [19] as a consequence of sodium deficiency remains in the central nervous system in an attenuated form after sodium balance has been restored. This memory may effectively alter behavior to cause enhanced seeking and ingestion of salty foods. If this is true, then, many of the neural processes that are responsible for sodium appetite (e.g., changes in neurotransmitter release, messenger RNA (mRNA) expression, or receptor expression) should still be exhibited long after body sodium has been restored. Recent evidence supports this idea as repeated episodes of sodium deficiency produce a long-lasting elevation in mRNA expression across the LT for the angiotensin II receptor type 1, mineralocorticoid receptor, and serum- and glucocorticoid-induced kinase, an intracellular messenger that is activated downstream from the mineralocorticoid receptor [60, 74, 102]. Additionally, sodium depletion appears to produce a long-lasting increase in the expression of ΔfosB, a molecular marker that has been associated with neural plasticity, in the SFO [60, 103, 104].

Perspectives on the sensitization of sodium appetite

It is important to realize that the sensitization of sodium appetite can be conceived of as an adaptive form of simple, non-associative learning that aids animals in maintaining sodium balance when faced with environmental conditions and challenges that threaten body sodium content. When body sodium content is repeatedly depleted, it is adaptive for an animal to seek out and ingest greater amounts of salt to help restore sodium balance and to protect against future sodium loss [41]. For example, humans working in hot environments

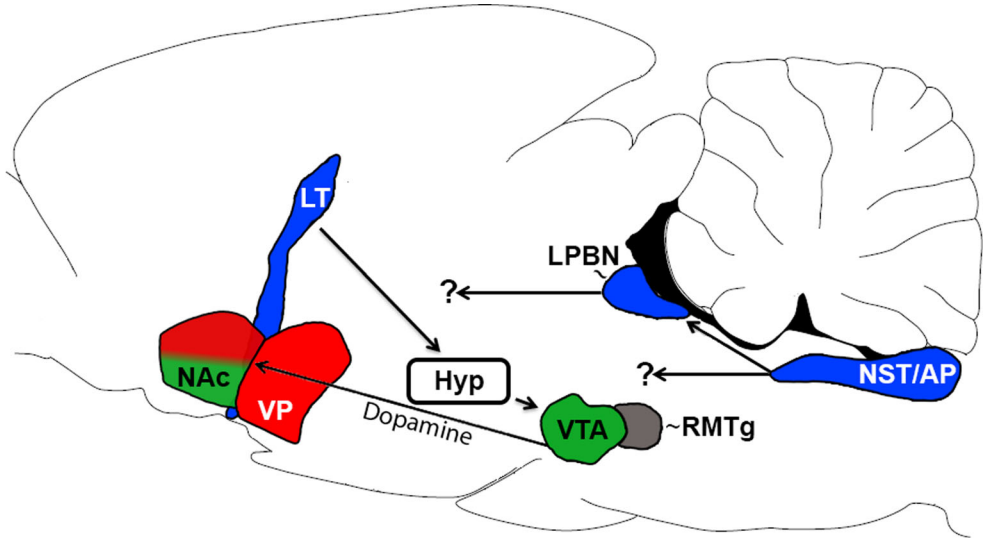

Fig. 2 The neural circuitry that mediates the various aspects of the biopsychology of salt appetite and sodium depletion. *Regions in blue* represent areas that play a role in detecting and communicating deficiency in mineralo-fluid balance or a decrease in blood pressure. *Areas in green* are likely to be involved in promoting goal-directed behavior towards salt (i.e., a desire for salty substances). *Areas in red* appear to code the rewarding effect of ingesting salty foods. The NAc is highlighted in both *green* and *red* because it contains sub-regions that promote goal-directed behavior and reward [110]. Finally, it is proposed that the rostromedial tegmental nucleus (*RMTg*), outlined in *grey*, may mediate the aversive effects of sodium deficiency [63]. The NTS and LPBN are likely to project to and influence activity of forebrain and midbrain nuclei that mediate motivated behavior and hedonics [34, 67]. The lamina terminalis appears to project to neurons in the hypothalamus which may serve to integrate body fluid status with motivation and reward systems such as the VTA [58]. The VTA, in turn, sends dopaminergic projections to the nucleus accumbens that mediate salt craving [4]. It is possible that opioid release in the dorsomedial accumbens is involved in the rewarding aspects of salt ingestion [83–85, 100, 110]. Abbreviations and a brief description of brain areas are presented in Table 1. The outline of the rat brain is derived from [108]

can lose significant quantities of sodium through sweat [2, 11, 98] and it would be ideal for these individuals to develop a propensity to ingest salty foods to protect and restore sodium balance. However, a negative consequence of sodium appetite sensitization is that it could promote pathological salt intake that may contribute to the development of many disorders [86] including cardiovascular disease.

Conclusions

Sodium depletion has a broad range of effects on psychology. A summary of the neural circuitry involved in the psychology of salt appetite and sodium deficiency is presented in Fig. 2 and Table 1. Sodium deficiency causes animals to crave salty substances and evaluate salt as more rewarding [3, 6, 19].

Table 1 Table associated with Fig. 2

Abbreviation	Description
Hyp	Hypothalamus—structures along the LT project to the hypothalamus and the hypothalamus contains dense projections to the VTA. It is likely that the hypothalamus aids in integrating signaling from the LT related to body fluid status with the mesolimbic dopamine system.
LPBN	Lateral parabrachial nucleus—an area in the hindbrain that appears to chronically inhibit sodium appetite. Disinhibition of this region results in a robust salt appetite.
LT	Lamina terminalis—a region of the forebrain that contains nuclei that detect disturbances in fluid balance and initiate thirst and salt appetite.
NAc	Nucleus accumbens—a region that has been implicated in the control of motivated behaviors. Dopaminergic projections from the VTA promote craving for rewards in the environment. Opioid release in the dorsomedial accumbens appears to promote reward.
NST/AP	Nucleus of the solitary tract/area postrema—a region in the hindbrain that receives afferents from baroreceptors and detects peripheral signals related to fluid balance.
RMTg	Rostromedial tegmental nucleus—a region of the midbrain that appears to code aversion. This structure inhibits dopamine neurons in the VTA.
VP	Ventral pallidum—a region of the forebrain that is involved in coding reward.
VTA	Ventral tegmental area—an area of the midbrain that contains the dopamine neurons that project to the nucleus accumbens.

Detection of sodium status involves systemic baroreceptors and centrally the SFO, AP, and NST [67]. The mesolimbic dopamine system and the VP are apparently involved in the motivational and rewarding aspects associated with sodium deficiency and repletion [57, 101, 117]. It is likely that the mesolimbic dopamine system drives salt craving and the VP promotes salt liking [4]. It is also possible that opioid activity in the dorsomedial region of the NAc promotes salt liking [100, 110] Sodium deficiency also appears to induce negative effects on cognitive function and may induce fatigue and depressive-like symptoms [52, 88, 89, 96–98]. The neural substrates mediating the negative effects of sodium deficiency can only be speculated upon at this point. One region of the brain that may contribute to the anhedonia-like behavioral changes associated with sodium depletion is the rostromedial tegmental nucleus (RMTg), an area that has received significant attention for its role in coding aversion and antagonizing the mesolimbic dopamine system [56, 63]. Finally, sodium depletion may produce long-lasting changes in the neural circuitry that codes the incentive value of salt [101, 118] and this plasticity may ultimately cause animals to seek out and ingest a greater quantity of sodium.

Acknowledgments The authors thank Marilyn Dennis for comments on the manuscript and reviewers for the helpful comments on earlier manuscript submissions. This research was supported by National Institutes of Health grants HL14388, HL098207, and MH08241.

Conflict of interest The authors have no disclosures to report.

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