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Mineralocorticoid-induced sodium appetite and renal salt retention: Evidence for common signaling and effector mechanisms

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Abstract

An increase in renal sodium chloride (salt) retention and an increase in sodium appetite is the body's response to salt restriction or depletion in order to restore salt balance. Renal salt retention and increased sodium appetite can also be maladaptive and sustain the pathophysiology in conditions like salt-sensitive hypertension and chronic heart failure. Here we review the central role of the mineralocorticoid aldosterone in both the increase in renal salt reabsorption and sodium appetite. We discuss the working hypothesis that aldosterone activates similar signaling and effector mechanisms in the kidney and brain, including the mineralocorticoid receptor, the serum- and-glucocorticoid-induced kinase SGK1, the ubiquitin ligase NEDD4-2, and the epithelial sodium channel ENaC. The latter also mediates the gustatory salt sensing in the tongue, which is required for the manifestation of increased salt intake. Effects of aldosterone on both brain and kidney synergize with the effects of angiotensin II. Thus, mineralocorticoids appear to induce similar molecular pathways in the kidney, brain, and possibly tongue, which could provide opportunities for more effective therapeutic interventions. Inhibition of renal salt reabsorption is compensated by stimulation of salt appetite and vice versa; targeting both mechanisms should be more effective. Inhibiting the arousal to consume salty food may improve a patient's compliance to reducing salt intake. While a better understanding of the molecular mechanisms is needed and will provide new options, current pharmacological interventions that target both salt retention and sodium appetite include mineralocorticoid receptor antagonists and potentially inhibitors of angiotensin II and ENaC.

Keywords

aldosterone; salt intake; hypertension; kidney; brain; tongue; mineralocorticoid receptor; ENaC; salt appetite; angiotensin II; NEDD4-2; SGK1; sodium reabsorption

Introduction

Sodium chloride (salt) homeostasis depends on the balance of salt intake and excretion, the latter being primarily mediated by the kidneys. Impaired renal salt excretion combined with excess salt intake can cause arterial hypertension, a leading cause of cardiovascular death [1]. Much has been learned about the molecular mechanisms and genetics that regulate renal salt reabsorption and excretion. The molecular determinants of salt intake, however, are still poorly understood. Salt intake is known to vary significantly from person to person, and, at least in part through its positive association with blood pressure, is a risk factor for non-diabetic chronic kidney disease [2]. In comparison, salt intake has been negatively correlated with renal outcome and mortality in patients with diabetes [3]. These findings underline the need to better understand the determinants of salt intake.

“Sodium appetite”, i.e. the preference for salty food and fluid, is one factor that contributes to salt intake. In this review we discuss the regulation of sodium appetite by mineralocorticoids. More specifically, we propose that mineralocorticoid-induced sodium appetite in the brain shares some of the molecular mechanisms that mediate the salt-retaining effect of mineralocorticoids in the kidney. We will first introduce the general phenomenon of sodium appetite (for excellent reviews see [4, 5]). We will briefly discuss well-established signaling pathways and effectors involved in renal actions of mineralocorticoids and then explore their roles in sodium appetite. Patients with diseases like congestive heart failure, salt-sensitive hypertension, liver or kidney failure are often non-compliant with regard to the recommendation of eating a low-sodium diet [6, 7]. This is in part due to the underlying pathophysiology, which may induce sodium appetite [8-12]. A better understanding of the determinants and molecular mechanisms of sodium appetite may provide new preventive and therapeutic avenues.

Salt intake and the phenomenon of sodium appetite

The total volume of extracellular fluid in the body depends largely upon the amount of sodium present in the extracellular space. Normal growth requires the ingestion and retention of sodium. Associated water input and output are adjusted to tightly control osmotic pressure. The Institute of Medicine set the adequate intake for sodium in young adults at 1.5 g (65 mmol)/day (3.8 g of salt). Further recommendations include a tolerable upper limit for sodium intake of 2.3 g (100 mmol)/day (5.8 g of salt) at 14 years (http://www.nal.usda.gov/fnic/DRI/DRI_Water/water_full_report.pdf). Based on the latter recommendation, in 2009-2010 about 80% of the U.S. population aged 1 year consumed excess sodium with a mean intake of 3.4 g/day (8.5 g of salt) (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6250a1.htm>).

Sodium appetite is a highly motivated behavioral state and hard-wired regulatory mechanism that drives animals [13, 14] and humans [11, 15-18] to seek and ingest foods and fluids containing sodium. This occurs in conditions of negative salt balance, such as dietary salt deprivation or loss due to excessive sweating, impaired renal sodium retention (Gitelman's syndrome) or impaired aldosterone formation (mutation in 21 β -hydroxylase), as well as after peritoneal dialysis, diarrhea, or diuretic treatment, when it is an essential behavioral mechanism to restore salt balance. In accordance with its importance, sodium-

deprived rats choose the taste of sodium over moderate intensities of directly rewarding brain stimulation [19]. Notably, the appetite stimulated by salt deficiency is highly specific for the taste of sodium salts [20] and the paired anion (chloride, acetate, etc.) has little or no effect on this preference [21].

Together with thirst, sodium appetite is critical for restoring extracellular fluid and preserving life. The sodium concentration in the cerebral spinal fluid (CSF) is positively related to its plasma concentration [22], and an increased CSF sodium concentration stimulates thirst [23] and inhibits sodium appetite [24-26]. The latter response involves the sodium sensor, NaX [27] (Figure 1). NaX is located in forebrain circumventricular organs [28], a region that lacks a blood-brain barrier, and in many glial cells in the subfornical organ (SFO) and other parts of the lamina terminalis, which makes them uniquely sensitive to large increases in the extracellular sodium concentration [28-32]. In mice, NaX in the SFO is necessary for the rapid stimulation of thirst by hypertonic saline infusion, as well as the inhibition of salt intake after 24h water deprivation [28, 31]. This channel, however, seems unlikely to sense subnormal sodium concentrations or salt depletion. Furthermore, whether a reduction in intracerebroventricular (icv) fluid sodium concentration increases sodium appetite remains unclear. Circumstantial evidence has been published in sheep [24, 25], and a sodium sensor proposed [25, 33, 34], but the nature of this hypothetical low-sodium sensor remains unknown and the findings could not be confirmed in rabbits, rats, and mice [35-37].

The pioneering work by Curt Richter established the phenomenon of sodium appetite when he studied the responses in rats following removal of the adrenal glands; he further showed that continuous dietary supplementation of sodium is required to prevent death following removal or gross dysfunction of the adrenal glands, and that saline intake returned to normal when functional adrenal tissue was transplanted back [14, 18, 20]. Subsequent studies showed that replacement-doses of mineralocorticoids, including aldosterone [38, 39], mimicked this effect of re-transplantation. These studies introduced a role of mineralocorticoids in the stimulation of sodium appetite. The clinical relevance was further illustrated in a case report by Wilkins and Richter in 1940 that described the severe salt cravings of a boy from a very early age; this boy had undiagnosed cortico-adrenal insufficiency and his life, like Richter's adrenalectomized rats, depended on the continuous intake of sodium, and he died after being denied access to salt during hospitalization [18]. Subsequent studies refined the system indicating that angiotensin II, baroreceptors, cerebral osmoreceptors, and other neurohormones modulate the aldosterone-induced arousal of sodium appetite [4, 5].

Mineralocorticoids stimulate renal salt reabsorption

The strongest stimulator for the secretion of aldosterone from the adrenal gland is salt loss and volume depletion, which occurs independent of circulating angiotensin II levels [40-42], although the latter can also stimulate aldosterone release (Figure 1). Aldosterone binds to the mineralocorticoid receptor (MR) expressed in a variety of tissues including the distal convoluted tubule, connecting tubule, and collecting duct of the kidney [43-45] to induce salt retention. In more detail, translocation of ligand-bound MR to the nucleus activates gene

transcription of multiple genes including the serum-and-glucocorticoid-induced kinase SGK1, which contributes to enhancing the expression of the α -subunit of the basolateral expressed Na, K-ATPase as well as the α -subunit of the apical expressed epithelial sodium channel (ENaC) [46,47]. Upregulation of ENaC involves SGK1-mediated relieve of Dot1a-Af9-mediated transcriptional repression of ENaC α [48]. Ubiquitination of ENaC by the ubiquitin ligase, neural precursor cell expressed and developmentally down regulated 4-2 (NEDD4-2), leads to ENaC retrieval from the apical membrane [49]. SGK1 phosphorylates NEDD4-2 and prevents NEDD4-2 to interact with ENaC, thereby enhancing the accumulation of ENaC at the plasma membrane for maximum activity (Figure 1). Aldosterone can also stimulate the Na-Cl cotransporter NCC in the distal convoluted tubule [50] and the Cl⁻-HCO₃⁻ exchanger pendrin in intercalated cells [51] to enhance reabsorption of Cl⁻. This upregulation of NCC likewise involves SGK1 and NEDD4-2 [50, 52].

Mineralocorticoids stimulate sodium appetite

Adrenalectomy induces renal salt loss and causes rats to drink large amounts of saline to maintain salt balance, implying compensation by aldosterone-independent mechanisms. Substituting low doses of mineralocorticoids in these rats reduced renal salt excretion and saline intake [38, 53-55]; aldosterone levels around 85 pg/ml, which is well within the physiological range, resulted in the lowest saline intake [54]. Higher mineralocorticoid doses increased saline intake in adrenalectomized rats [38, 55]. High doses of the mineralocorticoid desoxycorticosterone acetate (DOCA) or aldosterone also increased saline intake in rats [38, 56, 57], mice [58, 59], and primates [60] with intact adrenal glands. Humans have also demonstrated preference for salt in certain conditions such as following extensive exercise or other causes of enhanced or abnormal aldosterone production [61, 62].

Mineralocorticoid receptors in brain mediate stimulation of sodium appetite

Hypernatremia inhibits salt intake [26, 28, 63, 64](Figure 1). In comparison, plasma sodium levels are often unaltered during sodium depletion, and hyponatremia is neither necessary nor sufficient for stimulating sodium appetite [4, 5](see also discussion above), indicating that the signal of sodium depletion is transmitted to the brain by other means. MRs are widely expressed in the brain, including the choroid plexus, hippocampus, some hypothalamic nuclei, amygdala, circumventricular organs, brain stem, cerebellum, and cortex [65-67]. Studies in rats showed that chronic infusion of aldosterone into the 4th ventricle increased the daily salt intake [68]. Vice versa, injection of the MR antagonist RU 28318 into the 4th ventricle reduced the sodium appetite following loop diuretic-induced salt depletion [68]. Inhibition of saline intake was also shown by intracerebroventricular (icv) application of the MR antagonist spironolactone in an experimental model mimicking microgravity and bed rest [69] as well as in a chronic heart failure model [12]. Daily injection of DOCA directly into the amygdala increased saline intake in rats; this response was significantly inhibited by intracranial application of antisense oligodeoxynucleotides against MR, but not against the glucocorticoid receptor [70]. With regard to the dynamics of the system, direct application of DOCA or aldosterone into the amygdala increased saline intake within 15 minutes; pretreatment with a MR antagonist 1 hour prior inhibited the aldosterone-induced saline intake [70]. Such a rapid response is consistent with the observation that 1 hour of intense exercise increased the salt preference in human [61].

These studies implicated that activation of MR in the brain is critical for salt depletion-induced sodium appetite (Figure 1).

When in animals with salt depletion icv application of RU-28318 was combined with subcutaneous injection of captopril to suppress endogenous angiotensin II, sodium appetite was completely suppressed; in contrast, peripheral MR blockade did not decrease sodium appetite [71]. Intracerebral injection of angiotensin II is more effective on salt intake and magnifies the aldosterone effect; vice versa, the effect of angiotensin II is enhanced by mineralocorticosteroids [60, 72-74], indicating a strong synergy between aldosterone and angiotensin II. Thus, sodium appetite may be the result of simultaneous elevations in peripheral aldosterone and angiotensin II produced by the brain's own renin-angiotensin-system [72, 75](Figure 1). Notably and in contrast to angiotensin II, which stimulates water and sodium intake [76], mineralocorticoids stimulate the intake of sodium with little or no effect on water intake [56,59,77], which may facilitate differential regulation of water and sodium intake.

Glucocorticoids can also bind and activate the MR. In physiological conditions, the circulating concentration of active glucocorticoids is 100- to 1000-fold higher than that of aldosterone. To protect the MR from inappropriate activation by glucocorticoids, 11 β -hydroxysteroid dehydrogenase type 2 (HSD2) is locally expressed to inactivate these glucocorticoids [78]. In accordance, a pronounced increase in sodium appetite was reported in a patient with impaired HSD2 function [79]. Expression of HSD2 has been detected in blood vessel walls and in epithelial cells of the distal nephron, colon, and sweat glands, i.e. in organs of high aldosterone sensitivity. HSD2 expression has been detected in the brain of rats and mice including the nucleus tractus solitarius (NTS) [80-82]. Potential candidates for mediating the induction of sodium appetite include the neurons in the NTS that co-express MR and HSD2 (Figure 1) and are activated (increase in nuclear c-Fos) by chronic salt deprivation and inactivated following salt repletion [83]. These neurons, like sodium appetite, can still be activated by dietary sodium deprivation after adrenalectomy, indicating that they integrate other signals in addition to aldosterone [84]. In addition to aldosterone and angiotensin II, multiple endogenous neuromodulators have been implicated in the regulation of sodium appetite but their relevance has not been unequivocally established [4, 5].

SGK1 mediates mineralocorticoid-induced salt appetite

SGK1 is induced by serum and glucocorticoids as well as many other stimuli including aldosterone and changes in cell volume (for review see [47]). It is expressed and induced by mineralocorticoids in a variety of tissues including the kidney, colon, and heart [47]. In human brain, northern blot analysis showed SGK1 to be expressed in amygdala, caudate nucleus, corpus callosum, hippocampus, substantia nigra, subthalamic nucleus, and thalamus [85]. Cerebral SGK1 is upregulated by glucocorticoids and corticotropin releasing hormone, and its function has been linked to pathophysiological changes in the central nervous system [86]. Notably, the expression of SGK1 in the choroid plexus of stroke-prone spontaneously hypertensive rats was upregulated by a high salt diet and this response was attenuated by icv

infusion of the MR antagonist eplerenone [87], indicating MR-induced SGK1 in the choroid plexus.

SGK1 mediates DOCA-induced sodium appetite [59]. When given the choice of drinking tap water or 1% saline, subcutaneous implantation of a DOCA-releasing pellet significantly increased drinking of saline versus tap water in wild type (WT) mice, consistent with DOCA-induced sodium appetite. This response was reduced or prevented in SGK1 knockout (-/-) mice [59]. In accordance, the preference of pregnant mice to drink a NaCl-solution was reduced when SGK1 was deleted despite of higher plasma aldosterone concentrations compared with WT mice [88].

Is brain ENaC involved in mineralocorticoid-induced sodium appetite?

In the brain of humans and monkeys, ENaC δ is the predominantly expressed subunit [89]; in mouse and rat, however, the δ -subunit appears to be a pseudogene and the other 3 subunits α , β and γ are predominant. In rat brain, co-expression of ENaC α , β and γ have been detected in the cardiovascular regulatory centers including the magnocellular neurons (MNCs) in the supraoptic nucleus (SON) and the paraventricular nucleus (PVN), in the median preoptic nucleus (MnPO), cingular and piriform cortex, and the hippocampus [67]. The study of adjacent sections suggested that all three ENaC subunits were co-expressed with MR in the same groups of cells in these regions. In areas such as the SFO, immunoreactivity was prominent only for the α - and β -subunits of ENaC and MR whereas γ -ENaC was not detected; immunoreactivity for α - and β -ENaC subunits in these regions usually paralleled MR positivity, and colocalized well with neuron marker positive cells [67]. The three ENaC subunits and MR were also colocalized in vasopressin and oxytocin-positive cells in the SON and PVN in rats [90]. Single cell PCR confirmed mRNA co-expression of all three ENaC subunits and MR in MNCs from those areas, and, by using the ENaC blocker benzamil, indirect evidence was provided that ENaCs can affect the firing patterns of MNCs [90]. Studies in mice confirmed the expression of all three ENaC subunits in cortex, choroid plexus, SFO, SON, and PVN [91]. Thus, where studied, co-expression of ENaC subunits and MR has been regularly confirmed in the central nervous system, a prerequisite for the regulation of ENaC by aldosterone (Figure 1).

As introduced above, ENaC is ubiquitinated by NEDD4-2, which marks ENaC for internalization in the kidney. In accordance, *Nedd4-2*^{-/-} mice have increased plasma membrane expression of ENaC subunits in the distal nephron and collecting duct [92]. Notably, Leenen's group described that these mice also have increased expression of ENaC subunits in the cytoplasm and plasma membranes in the central nervous system including neurons and the choroid plexus [91](Figure 1). Moreover, acute icv infusion of sodium-rich CSF increased arterial blood pressure by around 10 mmHg in WT mice, while in *Nedd4-2*^{-/-} mice, the blood pressure increased by 25-30 mmHg (Figure 1). This enhancement was abolished by icv infusion of the ENaC inhibitor, benzamil [91]. The group further found that a high salt diet increased the sodium concentrations in CSF in *Nedd4-2*^{-/-} but not in WT mice. Finally, the high salt diet increased mean blood pressure by 30 to 35 mmHg in *Nedd4-2*^{-/-} mice, a response largely prevented by icv benzamil but only to a minor extent by subcutaneous benzamil at the icv rate [91]. Leenen and coworkers concluded that increased

ENaC expression in the brain of *Nedd4-2^{-/-}* mice mediates their hypertensive response to a high salt diet by increasing sodium concentrations in the CSF, as well as hyperresponsiveness to CSF sodium (Figure 1). Similarly, chronic icv infusion of benzamil abolished the sympathetic hyperactivity and hypertension caused by chronic icv infusion of sodium-rich CSF or by high salt diet in Dahl salt-sensitive (S) rats [93]. Dahl S also exhibited an increase in CSF sodium concentration in response to a high salt diet [94], as well as enhanced sympathoexcitatory and pressor responses to increasing sodium concentration in CSF [95], thus mimicking the phenotype of *Nedd4-2^{-/-}* mice. Together these findings suggest a possible role of ENaC in sodium regulation in brain and in the etiology of high salt diet-induced hypertension. Further studies are needed, however, to more specifically test the role of brain ENaC in this regard and for mineralocorticoid-induced salt appetite. Dietary sodium inhibits the open probability of ENaC in the kidney by enhancing apical ATP/UTP release and P2Y₂ receptor activation [96]. Mice lacking this receptor present DOCA-induced salt-sensitive hypertension associated with salt aversion when given access to tap water and 1% NaCl solution [96]. It remains to be determined whether the ATP/UTP/P2Y₂ receptor system regulates brain ENaC and CSF sodium concentrations.

Sensing of salty food and fluid via ENaC in tongue

Sodium-deficient rats cannot discriminate saline from other solutions when gustatory sodium channels were blocked [97-99]. ENaC is expressed in the gustatory system where it contributes to salt sensing during salt deprivation. Conditional knockdown of ENaC α in all taste-receptor cells of the tongue prevented amiloride-sensitive sodium uptake in the low NaCl concentration range, while these animals retained the normal responses to non-sodium salts [100]. Furthermore, whereas diuretic-induced sodium depletion induced sodium appetite in WT, mice with ENaC α knockdown in the tongue showed little or no preference for NaCl solutions relative to water [100]. These studies indicated that salt depletion-induced sodium appetite uses ENaC-mediated Na⁺ uptake in tongue epithelia to identify dietary salt sources (Figure 1). To our knowledge, the expression of MR, SGK1, or NEDD4-2 in tongue or the effects of aldosterone or angiotensin II on ENaC have not been studied.

Geering and Loewy have proposed a model with three central components to explain the induction of sodium appetite following salt depletion [4, 83, 101]. First, during salt depletion, specific groups of neurons (see candidates in NTS above) provide signals for sodium need that motivate salt-seeking behavior. Second, once sodium is tasted (see above), the gustatory apparatus transmits a signal representing sodium detection. Third, these two signals are integrated (along with inhibitory signals that promote sodium aversion) in one or more forebrain sites (possibly including the nucleus accumbens and a dopamine-dependent motivational signal for salt intake) that ultimately drive motivated ingestive behavior (Figure 1).

Summary and perspectives

The body responds to salt restriction or depletion with an increase in renal salt retention and an increase in sodium appetite to restore salt balance. Both mechanisms involve the

mineralocorticoid, aldosterone. By activation of the MR in the aldosterone-sensitive distal nephron, aldosterone induces early transcriptional up-regulation of SGK1 expression. SGK1 stimulates basolateral Na-K-ATPase, increases the expression of ENaC, and suppresses the activity of the ubiquitin ligase NEDD4-2 to retain ENaC in the luminal membrane and maximize ENaC activity and sodium reabsorption. The induction of sodium appetite by aldosterone in the brain involves a similar molecular pattern. A role for the MR and SGK1 in mineralocorticoid-induced sodium appetite has been established. The aldosterone sensitivity, sodium appetite-associated activation and input/output connections of neurons that co-express the MR and HSD2 implicated these neurons in the NTS in the induction of sodium appetite. NEDD4-2 has been implicated in the regulation of ENaC in brain thereby affecting sodium concentrations in CSF and blood pressure. Effects of aldosterone on both brain and kidney synergize with the effects of angiotensin II. The induction of salt intake also relies on gustatory salt sensing mechanisms in the tongue that involve ENaC in taste buds.

Thus, mechanisms that regulate salt homeostasis via effects on the kidney, brain, and tongue share some of the molecular pathways, yet many issues need further clarification. It remains to be determined whether aldosterone regulates ENaC in brain and whether this contributes to sodium appetite. How does brain ENaC affect the sodium concentration in CSF, and does ENaC mediate effects of increased CSF sodium on blood pressure? We need to better understand how aldosterone influences these unique neurons at the cellular and local-circuit levels. Does aldosterone (via MR activation) or angiotensin II affect ENaC in the tongue and what are the downstream signaling cascades of ENaC-mediated sodium sensing? More data are needed regarding the regulation of sodium appetite in humans and its relevance in various disease states.

Common molecular pathways may provide the opportunity for more effective therapeutic intervention. In other words, a drug targeting a molecule common to both pathways allows to inhibit renal salt retention and sodium appetite at the same time. Inhibition of renal salt reabsorption is compensated by stimulation of sodium appetite and vice versa. Therefore, inhibiting both mechanisms should be more effective. Inhibiting the arousal to consume salty food or fluid may improve a patient's compliance to reducing salt intake. This may be relevant in patients with salt-sensitive hypertension or chronic heart failure, and animal models provided first evidence for salt appetite under these conditions [9, 12]. Potential candidates for pharmacological interventions that can inhibit both renal sodium retention and sodium appetite include drugs that have been shown to provide long-term health benefits in patients, such as mineralocorticoid receptor antagonists or inhibitors of angiotensin II, and their combination could be particularly effective in this regard. Additional candidates include inhibitors of ENaC. A better understanding of the molecular mechanisms is needed, which holds the potential for new therapeutic approaches.

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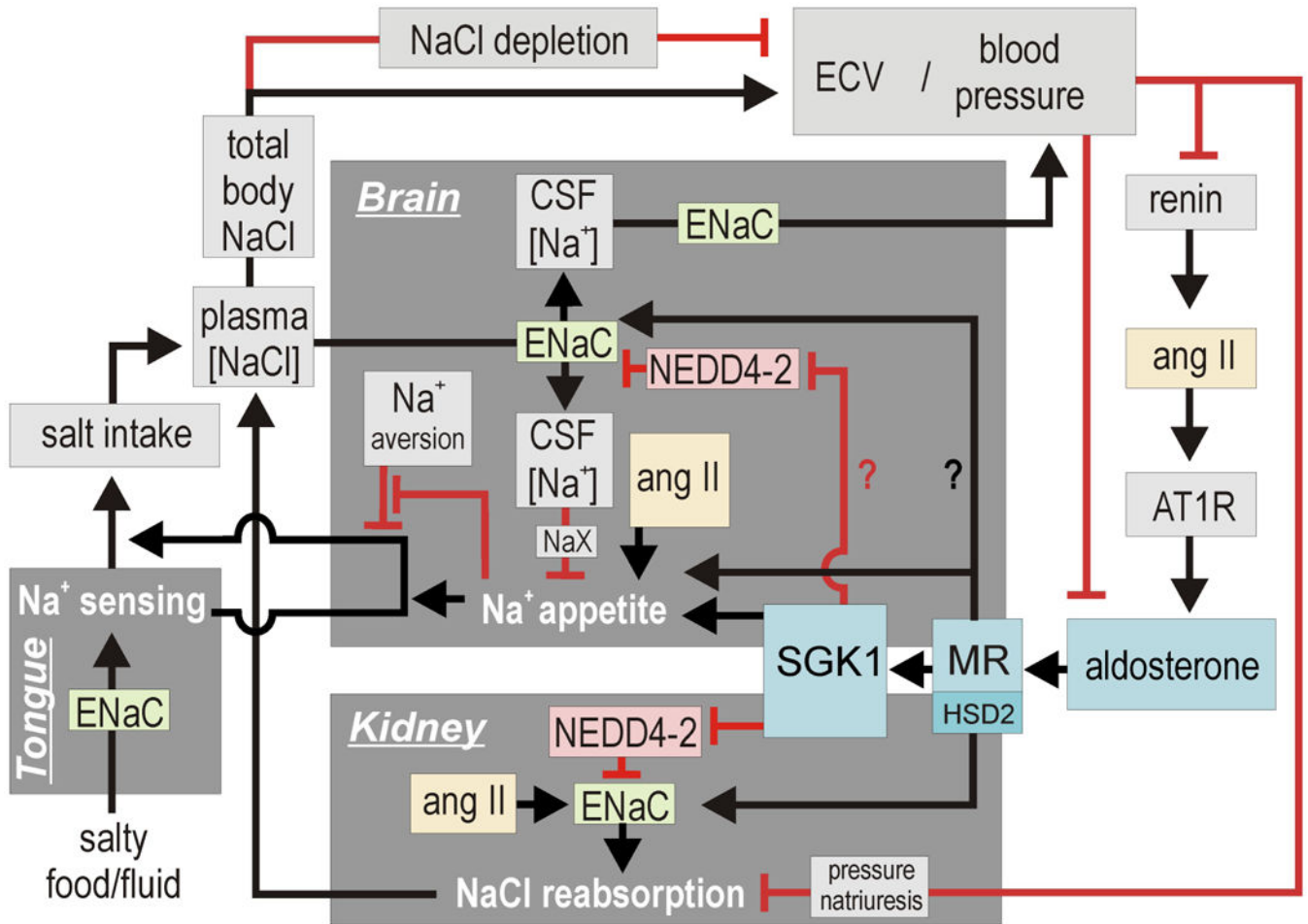


Figure 1. Proposed central role of the mineralocorticoid aldosterone in salt homeostasis through its effects on both the increase in renal salt reabsorption and sodium appetite

Aldosterone activates similar molecular mechanisms in the kidney and brain, including the mineralocorticoid receptor (MR) and the serum-and-glucocorticoid-induced kinase SGK1. The ubiquitin ligase NEDD4-2 and the epithelial sodium channel ENaC have also both been implicated in salt homeostasis in kidney and brain. ENaC also mediates the gustatory sodium sensing in the tongue, which together with inhibition of sodium aversion is required for the manifestation of sodium appetite-induced increase in salt intake. Effects of aldosterone on both brain and kidney synergize with the effects of angiotensin II (ang II). Inhibition of renal salt reabsorption is compensated by stimulation of salt appetite and vice versa. Therefore, inhibiting both mechanisms has advantages. Current pharmacological interventions that target salt retention and appetite include MR antagonists, and potentially inhibitors of angiotensin II and ENaC. See text for further details. AT1R, angiotensin II AT1 receptor; CSF, cerebral spinal fluid; ECV, effective circulating volume; HSD2, 11 β -hydroxysteroid dehydrogenase type 2; NaX, sodium sensor.