Salt appetite and addiction—unholy twins?

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Many behavioural patterns are dependent on neural mechanisms that are of high survival value. Liedtke et al. [1] (http://www.pnas.org/content/108/30/12509.long) studied one such example, i.e. sodium appetite, which is seen in herbivores and omnivores, but not in carnivores which can ‘gratify’ their salt needs by consuming meat. The neuronal organization of instinctive behaviours is known to be mainly located in the hypothalamus. In the present study, the authors observed that sodium-deficient mice develop a sodium-specific appetite when they are sodium depleted [2]; such sodium craving can be reproduced by administering adrenocorticotropic hormone (ACTH) [3]. The authors used this model of sodium-craving mice caused by sodium depletion or by infusion of ACTH; in addition, they also studied mice which after induction of sodium craving were offered 0.3 M NaCl.

Salty fluid offered to sodium-depleted mice was rapidly taken up and sodium repletion was completed within 10 min. In this model, the authors used genome-wide microarray techniques to compare the effects of sodium deficiency with those after sodium repletion. To their surprise, they found that the gene sets in the lateral hypothalamus which were involved in the regulation of sodium appetite and its gratification were identical with the gene sets associated with cocaine and opiate addiction. Using the technique of genome-wide microarrays, Liedtke et al. [1] documented the involvement of specific hypothalamic genes, particularly DARPP-32 (dopamine-and-CAMP-regulated neuronal phosphoprotein), STEP (striatally enriched protein tyrosine phosphatase), ARC (activity-regulated cytoskeleton-associated protein) and others. In sodium-depleted mice, up-regulation of these genes was almost instantly reversed as...
soon as 10 min after drinking 0.3 M NaCl: obviously a specific fast response to the sodium intake.

Surprisingly, such coregulation of the components of this gene pattern corresponded exactly to what had previously been documented in similar microarray studies of the reward pathways involved in models of opiate and cocaine addiction [4]. The authors drew the conclusion that the genes associated with these addictions are actually shared between sodium depletion and opiate or cocaine addiction, respectively.

The authors went one step further and assessed the protein expression of DARPP-32 which was known to be of critical relevance in the reward pathway of dopaminergic signalling [5, 6]. This signalling molecule is expressed in suprachiasmatic and supraoptic neurons, respectively, in both sodium-depleted and control mice; in contrast, in sodium-depleted rats, it is up-regulated in the periventricular nuclei and the lateral hypothalamus in those cells which coexpress orexin (19). Orexin is a neuropeptide which is involved in eating behaviour (σεξίζε = appetite), in the day–night cycle, in body temperature control, in alertness etc. and plays a role in alcoholism as well [7]. Liedtke et al. [1] proposed the hypothesis that a hypothalamic gene regulatory programme subserves sodium appetite and is involved in salt appetite gratification. While the phenomenon of gratification by rapid consumption of salt had before been shown in many experiments, the novel aspect in the present experiment is the analysis of hypothalamic gene expression changes evoked by sodium appetite and its gratification.

In addition, the authors decided to block the known hypothalamic regulatory programme for instinctive behaviour and reward pathways by administering selective antagonists of dopamine receptors and of the metabotropic glutamate receptor 5 which are involved in the drug reward pathways [8, 9]. The gratification behaviour is attenuated by both the dopamine D1 receptor and the dopamine 2(3) receptor pathway and therefore, the respective antagonists were examined. Both the D1(5) receptor antagonist and the D2(3) receptor antagonist reduced dose dependently the gratification behaviour, pointing to the causal role of these pathways. The specificity of this reaction was also documented by the observation that, for instance, water intake after intraperitoneal injection of hypertonic salt was not affected by D1(5) receptor blockade, suggesting that the dopamine-sensitive pathway is specific for salt appetite. Such specificity makes sense because non-specific reward reactions in hypothalamic control systems would create chaos: a hungry animal would not benefit from drinking water and a sexually aroused animal would not benefit from salt intake. To the surprise of the investigators, the genes regulating sodium appetite were enriched for gene sets associated with cocaine and opiate addiction [4]. This finding led the investigators to the hypothesis that the gene set involved in the defence against salt depletion had been ‘hijacked’ by these addictive compounds.

Of particular interest is the speed with which the reversal of sodium appetite occurs, i.e. within 10 min, in other words before salt resorption could have started in the gut. The authors argued that this may be biologically advantageous: in herbivores, such fast reversal of sodium appetite would provide better chances of survival by minimizing the risk of predation by carnivores while ingesting salt-containing fluid. It had been shown in the past that sodium-depleted sheep will rapidly drink 2–3 L of 300 mmol NaHCO₃ within 5 min; afterwards they lose interest in salt even before the absorption from the gut has taken place; similarly, camels can restore up to 10% of lost body weight within 10 min. The amazingly short time course makes biological sense since animals desperate to get water are an easy target for predators, so that shortening the time of ingestion minimizes the risk of predation by carnivores. This time course suggests that the hypothalamus receives information on the intake of salt water even before it has been absorbed in the gut. It is of note that in the tongue, there are sodium-specific amiloride-sensitive sodium sensors and these signals reach the brain via the trigeminal before the salt has been resorbed in the gut. So the fact that there are gene changes in the hypothalamus within 10 min after ingestion of NaCl makes biological sense.

The hypothalamic sensors for sodium are not unique and sensing in the hypothalamus by orexin/hypocretin neurons has recently been documented for amino acids and glucose [10] as well as for alcohol [7]. In the study of Burdakov [10], the neurons in the hypothalamus regulating energy balance and feeding were activated both in vitro and in vivo when exposed to nutritionally relevant amino acid mixtures [10]; glucose suppressed the activity of these neurons. Interestingly, the response was selective for amino acids: amino acids were excitatory and blocked the effect of glucose.

The question remains why the salt-sensing machinery in the hypothalamus is used by cocaine and opiates as well. The authors propose the plausible hypothesis that the ancient hypothalamic gratification machinery was devoted to guaranteeing sufficient sodium supply in herbivores and omnivores (and in primate times this included humans as well), thus providing high survival value. This contrasts with carnivores in which sodium supply is guaranteed by the consumption of meat. Extrapolating from their findings, the authors proposed the hypothesis that drug addiction may be explained by the assumption that the neuronal machinery which has helped to safeguard against salt depletion was ‘hijacked’ by the addictive compounds opium and cocaine.

What are the implications of these findings for humans, and more specifically, for the current controversy on optimum salt intake?

Common sense would suggest that too high as well as too low sodium intakes have adverse effects. The current controversy focuses on the issue of the optimum intake (if there is indeed an optimum which is the same for all individuals). Recently, revolutionary changes have occurred in our understanding of how the sodium-induced injury may be mediated, e.g. non-osmotic storage of sodium [11, 12] or the involvement of the adrenal steroid ouabain in sodium-mediated pathologies of renal failure [13, 14] to mention only a few. This ancient mechanism which might have been life-saving in our ancestors may explain why today, when access to salt is quasi unrestricted, current efforts to reduce salt intake are opposed with such vigour.

Conflict of interest statement. None declared.
References


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