

## Persistent Hunger for Sodium Makes Brain Stimulation Not So Sweet: Theoretical Comment on Morris et al. (2006)

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The rewarding value of a stimulus is not fixed but rather is subjective and can vary with motivational state. M. J. Morris, E. S. Na, A. J. Grippo, and A. K. Johnson (2006) report that generating a prolonged sodium appetite decreases the rewarding value of lateral hypothalamic brain stimulation and sucrose intake. The findings support the idea that a specific motivational state can have strong, nonspecific consequences for reward processing.

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Understanding the biology of how motivated state influences behavior has long been a topic of intense investigation, and progress on this front promises to advance the treatment of mood disorders, obesity, and drug addiction. Morris, Na, Grippo, and Johnson (2006) use a decades-old tool to ask a very novel and important question. That is, how do persistent perturbations in hormonal signaling affect reward processing? In 1954, Olds and Milner found that rats would press a lever to deliver current to particular regions of their brains—a phenomenon known as intracranial self-stimulation (ICSS). Morris et al. use this behavior to determine how frequently a rat will press a lever for different current intensities of stimulation, which indicates its subjective reward value. The resulting psychometric function is then compared with one generated following a change in motivated state. A shift in this curve indicates a change in the relative rewarding value of the stimulation. Morris et al. determined that a persistent increase in the desire to consume sodium, termed a *sodium appetite*, pushed psychometric curves to the right. That is, rats responded less for the same current intensity after days of an induced sodium appetite than before it or compared with rats receiving the treatment with the opportunity to consume sodium through intake. The data strongly suggest that a persistent sodium appetite results in a decrease in the rewarding value of stimuli that fail to satisfy the appetite—a conclusion supported by further experiments in their report that found sodium-depleted rats consumed less of a rewarding sucrose solution compared with controls.

Morris et al. (2006) placed stimulating electrodes in the lateral hypothalamus where they would activate dopaminergic fibers and cause the release of dopamine in the nucleus accumbens (Cheer et al., 2006; You, Chen, & Wise, 2001), which is believed to support the reinforcing properties of ICSS. Limbic circuitry and in particular the dopaminergic fibers of the ventral tegmental area and the nucleus accumbens appear to be substrates for the interaction of

sensory information with motivated state in the service of behavior. For example, several lines of research implicate accumbens dopamine signaling in the regulation of food intake. Food-predictive cues evoke an increase in dopamine within hundreds of milliseconds that peaks at the moment of the behavioral response to procure the food (Roitman, Stuber, Phillips, Wightman, & Carelli, 2004). Dopamine in the nucleus accumbens appears to be necessary and sufficient for rats to respond to food-predictive cues (Nicola, Taha, Kim, & Fields, 2005). Food deprivation increases dopamine release to the same food stimulus (Wilson, Nomikos, Collu, & Fibiger, 1995). Individual neurons within the nucleus accumbens exhibit changes in firing rate in response to food rewards, with the majority of food responses being inhibitions (Nicola, Yun, Wakabayashi, & Fields, 2004; Roitman, Wheeler, & Carelli, 2005; Taha & Fields, 2006). It is important to note that inhibiting the nucleus accumbens with either GABA agonists or glutamate antagonists can initiate robust feeding behavior even in sated rats (Kelley, 2004). This latter finding strongly suggests that motivational systems, when engaged, have the ability to initiate behavior even while homeostatic signals should prevent it (Berthoud, 2004; Kelley, Baldo, & Pratt, 2005).

For an animal to survive, it needs more than just food. It needs to maintain body fluid balance. Deviations from positive sodium balance can strongly engage motivational systems for sodium seeking. Acute sodium depletion changes rats' behavioral responses to concentrated sodium solutions. Under conditions of positive sodium balance, the taste of concentrated sodium solutions evokes orofacial responses similar to those of quinine or aversive taste stimuli. However, acute sodium depletion so dramatically alters behavior that orofacial responses to the very same sodium solutions are more like the responses observed to sucrose or rewarding taste stimuli (Berridge, Flynn, Schulkin, & Grill, 1984). Shizgal and colleagues (Conover, Woodside, & Shizgal, 1994) used a similar approach as Morris et al. (2006). They showed that acute sodium depletion did not cause curve shifts in responding for ICSS, suggesting that the rewarding value of the stimulation was unchanged following depletion. However, depletion did cause increased competition between responding for ICSS and responding for sodium (Conover, Woodside, & Shizgal,

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1994). The data suggest that the rewarding values of brain stimulation and sodium, under deplete conditions, were processed by similar, if not the same, neural substrates. Could dopamine and the nucleus accumbens contribute to the rewarding aspects of sodium for the sodium-depleted rat? Dopamine antagonists reduce the consumption of sodium solutions in the sodium-depleted rat (Roitman, Schafe, Thiele, & Bernstein, 1997). Sodium depletion and induction of a sodium appetite also alter dopamine and other signaling in the nucleus accumbens (Lucas, Grillo, & McEwen, 2003; Lucas, Pompei, Ono, & McEwen, 1998; Roitman, Patterson, Sakai, Bernstein, & Figlewicz, 1999). The nucleus accumbens, therefore, is a locus for depletion to exert its effects on sodium-seeking behavior.

Acute sodium depletion can have lasting effects on behavior. Rats, having been sodium depleted once before, consume significantly more of a concentrated sodium solution on subsequent depletions (Sakai, Fine, Epstein, & Frankmann, 1987) and under need-free conditions (Sakai, Frankmann, Fine, & Epstein, 1989). These effects mirror drug sensitization, whereby prior exposure to psychostimulants such as cocaine increases subsequent locomotor behavior evoked by a drug challenge. The nucleus accumbens and dopamine signaling are critical for drug sensitization (Berridge & Robinson, 1998; Robinson & Berridge, 2001). Sensitization to one stimulus can increase behavior evoked by another—a phenomenon called cross-sensitization. Could depletion episodes, which sensitize sodium-seeking behavior, lead to cross-sensitization with drugs of abuse? Indeed, they do, as evidenced by rats with a history of acute sodium depletion exhibiting increased behavioral activation from their first injection of amphetamine relative to rats with no history of depletion (Clark & Bernstein, 2004; Roitman, Na, Anderson, Jones, & Bernstein, 2002). In addition, a regimen of amphetamine injections that would lead to sensitization also sensitized sodium consumption following a single acute depletion relative to depleted rats with no history of amphetamine treatment (Clark & Bernstein, 2004). Multiple, acute depletions lead to structural changes in nucleus accumbens medium spiny neurons (Roitman et al., 2002) that are similar to the structural changes observed after a sensitizing regimen of amphetamine (Robinson & Kolb, 1997) or cocaine (Robinson & Kolb, 1999a) or after a period of cocaine self-administration (Robinson, Gorny, Mitton, & Kolb, 2001). Food restriction and deprivation also alter drug-mediated and drug-directed behavior (Cabib, Orsini, Le Moal, & Piazza, 2000). Important for this discussion, food restriction enhances the relative rewarding value of ICSS (Fulton, Woodside, & Shizgal, 2000). Together, the data suggest that deprivation states can have profound effects on reward-seeking behavior that generalize from the stimuli that satisfy the specific need to other rewarding agents.

Although deprivation states, including acute sodium depletion, seem to enhance the rewarding aspects of the stimulus that meets the need of the animal as well as stimuli that do not (e.g., ICSS and drugs of abuse; Carr, 2002), the work of Morris et al. (2006) investigates a chronic need state generated by prolonged exposure to a hormone agonist. The authors generated a persistent sodium appetite by chronic administration of a mineralocorticoid agonist (deoxycorticosterone acetate; DOCA). They showed that, if given the opportunity to ingest concentrated sodium solutions following these injections, rats avidly do so. The striking finding of Morris et al. is that generating a sodium appetite without the opportunity to

satisfy it for several days caused a rightward shift in the current–response function for ICSS of the lateral hypothalamus relative to pretreatment. This shift did not occur in saline-injected controls. More important, though, in rats that were given the exact same regimen of DOCA treatment but also permitted to consume a sodium solution, no shift was observed (see Figure 2 in Morris et al., 2006). The results demonstrate that the persistent or chronic sodium appetite caused by elevated steroid signaling can strongly influence reward processing by decreasing it. The effects of DOCA treatment were not limited to current–response functions. DOCA treatment over several days also suppressed sucrose consumption but only in rats that did not have the opportunity to consume a sodium solution over the treatment period. Thus, DOCA treatment altered the relative value of multiple rewards. Notably, if given the opportunity to consume a sodium solution following a period of DOCA treatment without access to sodium, rats still avidly ingested (see Figure 4 in Morris et al., 2006). Thus, although the rewarding value of stimuli that did not meet the perceived need diminished, the relative rewarding value of sodium remained intact. This likely reflects the interaction of multiple motivational systems: the dopamine–nucleus accumbens pathway being just one of them. For example, the circumventricular organs and even the amygdala are also important for thirst, sodium appetite, and body fluid homeostasis, and perhaps these other regions were sufficient to provide the neural signals required to overcome the decreased reward seeking due to effects of DOCA on the nucleus accumbens and dopamine signaling there. Understanding how sodium appetite is preserved in the face of decreased reward seeking remains a challenge for Morris et al. to address.

Several interesting questions remain. Shizgal and colleagues (Fulton et al., 2000) found that chronic food restriction caused leftward curve shifts in rate–frequency functions for ICSS but only at a subset of electrode placements. It is interesting that the hormone leptin, which induces reduced food intake and body weight, caused rightward curve shifts—but only at stimulation sites where food restriction was effective in inducing a leftward curve shift (Fulton et al., 2000). This study potentially mirrors the effects of sodium need. Acute sodium depletion was insufficient to alter responding for ICSS (Conover et al., 1994). As Morris et al. (2006) have shown, a chronic motivation for sodium is indeed effective in altering responding—pushing ICSS curves to the right. Moreover, both feeding and sodium consumption led to a return to baseline responding. It would be very interesting to determine whether food-restriction, and therefore leptin, sensitive sites in the lateral hypothalamus were also DOCA sensitive. That is, is there a subset of neurons activated by ICSS that are particularly sensitive to changes in a variety of motivational states?

Another potentially interesting intersection with the literature concerns structural changes within the nucleus accumbens. As mentioned above, both acute sodium depletion (Roitman et al., 2002) and psychostimulant administration (cocaine and amphetamine; Robinson & Kolb, 1999a) lead to increased dendritic arborization and spine density of medium spiny nucleus accumbens neurons. Repeated exposure to another abused drug, morphine, leads to opposite changes—medium spiny neurons exhibit decreased dendritic branching and spine density relative to controls (Robinson & Kolb, 1999b). It is interesting that during both morphine and nicotine withdrawal, thresholds for ICSS increased.

Rats required more current to engage in self-stimulation during withdrawal (Kenny & Markou, 2005; Schulteis, Markou, Gold, Stinus, & Koob, 1994), and thus the relative rewarding value of ICSS decreased. Given that chronic DOCA treatment also shifts relative reward, perhaps it would alter dendritic morphology in the nucleus accumbens in a manner more similar to morphine-treated than amphetamine-treated or acutely sodium-depleted rats.

Considerable work has focused on the role of glucocorticoids in reward, drug taking, and addiction. Investigation of the effects of mineralocorticoids, the other class of adrenal steroids, on reward has lagged behind. Morris et al. (2006) point out that human mood disorders can be linked to sodium dysregulation. Their study shows that a persistent sodium appetite generated by enhanced mineralocorticoid signaling decreases reward efficacy in rats. Lucas, Pompei, and McEwen (2000) have identified peptidergic changes in the nucleus accumbens that track the decrease in reward efficacy demonstrated by Morris et al. Further studies addressing the neurophysiological, neurochemical, and cellular changes associated with this effect, as well as the inclusion of associated brain regions such as the amygdala and the subdivisions of the prefrontal cortex, will undoubtedly shed considerable light on the etiology of mood disorders, drug addiction, and relapse.

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