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The Neuroscience of Pleasure. Focus on "Ventral Pallidum Firing Codes Hedonic Reward: When a Bad Taste Turns Good"

Robert A. Wheeler and Regina M. Carelli
Department of Psychology, The University of North Carolina, Chapel Hill, North Carolina

For more than 2,000 years, philosophers have struggled to define, let alone explain, pleasure or hedonics. With contemporary animal models and techniques, scientists now have the ability to provide a comprehensive description of this affective state by examining its neural underpinnings. In this issue of the *Journal of Neurophysiology* (p. 2399–2409), Tindell and colleagues use an elegant, reductionist approach to take a profound step in defining these neural foundations (Tindell 2006). The authors control for various elements of reward that historically have confounded researchers ambitious enough to attempt to study such an intangible topic.

Specifically, Tindell and colleagues establish a role for ventral pallidum (VP) neurons in encoding hedonics. The authors infused an unpalatable concentration of saline into the oral cavities of rats while recording the extracellular electrophysiological activity of single VP neurons. Aversive orofacial reactions to the unpalatable taste were simultaneously measured. Three days later, rats were made sodium deplete and retested. In a sodium-depleted state, these rats now exhibited a behavioral switch from aversive taste reactivity to appetitive taste reactivity coincident with increased VP activity to the infusion of saline (similar to responses for a palatable sucrose solution). The clever implicit controls indicate that the altered electrophysiological activity encodes a hedonic shift rather than alterations in motivated behavior or sensory coding.

Despite the proposal over a century ago that affective state can be determined by behavioral expression (Darwin 1898), this notion remains controversial. Perhaps the most intriguing aspect of the current study is the use of taste reactivity reflecting hedonics, or in the author's words, "liking." Although it has been argued that this interpretation is not strong enough (Panksepp 2005), it certainly advances the conclusions of the original studies of taste reactivity as ingestion and rejection responses, (i.e., a reflection of consummatory responses) that are sufficiently mediated by the caudal brain stem (Grill and Norgren 1978c). Recent pharamacological manipulations have shown that taste reactivity appears to be dissociable from consummatory behavior and is hierarchically modulated by rostral neural structures (Berridge 2000; Kelley and Berridge 2002). Taste reactivity also is distinct from motivated behavior. Rats increase appetitive taste reactivity for more palatable concentrations of intraorally infused solutions while increasing aversive taste reactivity to escalating concentrations of unpalatable tastants (Grill and Norgren 1978b). Likewise, taste reactivity is not a simple expression of reflexive sensation. When a rat learns that a sweet taste predicts illness, it doesn't just avoid the tastant, it exhibits rejection responses as if the sweet taste is now unpalatable (Grill and Norgren 1978a). Similarly, if a palatable taste is paired with an intragastric glucose infusion, appetitive taste reactivity increases (Myers and Sclafani 2001). Thus taste reactivity appears to be reflective of the rat's affective reaction to taste stimuli and therefore is a compelling measure of hedonics in non-humans (Berridge 2000).

Using this approach, Tindell and colleagues examined the role of the VP in hedonic coding. This nucleus is well situated to play a role in processing hedonic information, receiving fibers from the nucleus accumbens (NAc) and ventral tegmental area (VTA) while projecting to numerous nuclei including the NAc, VTA, amygdala, parabrachial nucleus, prefrontal cortex, and lateral hypothalamus (Groenewegen et al. 1993; Kalivas et al. 1999; Kelley 2004). Several studies, especially the author's own, indicate that this nucleus plays a role in motivation to seek drugs and natural rewards (McFarland and Kalivas 2001; Tindell et al. 2004, 2005). In addition to a role in motivated behavior, the VP appears to also have a specific role in the processing of hedonic information. For example the μ-opioid agonist, DAMGO, infused into a posterior subregion of the VP increases appetitive taste reactivity to sucrose, while ablation of this nucleus causes the emergence of aversive taste reactivity (Cromwell and Berridge 1993; Smith and Berridge 2005).

The current study is set apart from previous work with the use of the salt appetite design. Inducing a need state for salt alters the rat's neural and behavioral response to subsequent salt presentations. The use of this paradigm eliminates the possibility that the measured neural activity reflects motivated behavior or simply motor output as the salt solutions are intraorally infused by the experimenter. It also eliminates the issue of comparing stimuli that differ in more than hedonic valence, such as tastes of different saliencies or different tastes altogether, because the same salt solution is used throughout. Finally, it controls for the potential encoding of learned associations, such as a taste that predicts illness. Beyond simply controlling for possible confounds, the use of salt appetite builds on a rich literature detailing alterations of reward-related neural signaling in the NAc following the homeostatic challenge of salt need. The induction of salt appetite alters the morphology of NAc neurons and dopamine and enkephalin release into the NAc (Frankmann et al. 1994; Lucas et al. 2003; Roitman et al. 1999, 2002). Prior salt need also potentiates the behavioral response to amphetamine through alterations in D_2 dopamine receptor function (Clark and Bernstein 2006). In addition, the NAc itself is differentially responsive to natural and drug rewards, appetitive and aversive tastants, and reward devaluation (Carelli and Wightman 2004; Carelli et al. 2000; Roitman et al. 2005; Wheeler et al. 2005). These findings have broad implications because the VP is the recipient of D_2-expressing GABA/enkephalin efferents from the NAc (Lu et

Address for reprint requests and other correspondence: R. M. Carelli, Dept. of Psychology, CB 3270, Davie Hall, The University of North Carolina, Chapel Hill, Chapel Hill, NC 27599-3270 (E-mail: rcarelli@unc.edu).

al. 1997, 1998; Steiner and Gerfen 1998), suggesting that significant alterations in NAc neurotransmission are involved in the hedonic shift induced by salt appetite. The predominant response of NAc neurons to the appetitive tastant, sucrose, is a pronounced reduction in firing rate, whereas the predominant response to an aversive tastant, quinine, is an elevation in firing rate (Nicola et al. 2004; Roitman et al. 2005). This raises the possibility that NAc neurons have a disinhibitory role in hedonic encoding. That is, it appears likely that rewarding stimuli cause an inhibition of the GABA/enkephalin efferents to the VP that promotes the firing rate increase of VP neurons that encode positive hedonics, revealed by Tindell and colleagues. Moreover, sodium depletion causes an increase in dopamine/enkephalin transmission and a decrease in dopamine transporter activity in the NAc that should augment the disinhibition of the VP in a manner consistent with the present results (Frankmann et al. 1994; Lucas et al. 2003; Roitman et al. 1999). Also consistent with this possibility is the recent finding that GABA antagonist infusion into the VP increases saccharin consumption, whereas GABA agonist infusion decreases consumption and induces aversive taste reactivity (Shimura et al. 2006).

Further, it is likely that discrete subregions of the NAc-VP system differentially modulate the encoding of hedonics. For example, both the NAc and the VP contain specific areas where the μ-opioid agonist DAMGO augments positive hedonic responses to pleasurable stimuli (Pecina and Berridge 2005; Smith and Berridge 2005). Although several reports of subregion specificity have been made for the NAc, even on a single-cell level (Carelli and Wightman 2004), this is far less characterized in the VP. Future investigations of the functional compartmentalization within the VP are sure to reveal insights into hedonics, addiction and obesity. The present work contributes greatly to these endeavors. Beyond the implications for a broad common, but heterogeneous subregions mediating disease states, research of this kind has the potential to operationally define subjective concepts of affect that have thus far eluded description.

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