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Serotonin and Whisking

Rhythmic whisker movements, called "whisking," are produced by a brainstem central pattern generator (CPG) that uses serotonin to induce periodic firing in facial motorneurons. During active touch, motor cortex could regulate whisking frequency by controlling the rate of firing of the serotonergic neurons.

Who among the thousands of neuroscientists that daily work with mice or rats has not wondered "what motor makes those whiskers go"? In this issue of *Neuron*, Hattox et al. (2003) examine this question in detail, employing a range of experimental approaches to identify the brain mechanisms that mediate and regulate the characteristic rhythmic movements of facial whiskers, called "whisking." Whisking behavior is becoming particularly significant in light of rapid advancements in our understanding of the development, function, and plasticity of the whisker sensory system. At each level of the whisker-to-cortex pathway, whisker-related groups of neurons, termed "barrels" in the somatosensory cortex (Jones and Diamond, 1995; Woolsey and Van der Loos, 1970), constitute identifiable neural circuits whose secrets are becoming increasingly amenable to detailed study via a host of powerful in vivo and in vitro methodologies. Fascinating in its own right, the study of whisking may provide a powerful model for understanding other important rhythmic behaviors, including breathing, walking, chewing, and suckling.

Like other mammalian sensorimotor behaviors, whisking is a carefully regulated motor action linked intimately to the acquisition and processing of sensory information. During exploratory behavior, rats repetitively sweep their whiskers through the sensory environment in a rhythmic ~8 Hz pattern that is finely coordinated with body and head movements and with the respiration cycle (Welker, 1964). This allows objects of interest to be inspected not only with mechanical sensors on the face, including the whiskers, but also with taste receptors in the mouth and olfactory receptors in the nose.

Rats can use their whiskers to perform subtle texture discriminations at a level comparable to human and nonhuman primates using their fingertips (Carvell and Simons, 1990). During discriminative behavior, whisking produces relative motion between the palpated object and the sensory apparatus, a key feature of active touch in all mammals (see Lederman and Klatzky, 1987). The velocity range over which this occurs is similar to the speed of finger movements used by humans during texture discrimination. This range of relative motion velocities has also been found to be optimal for detection, by human observers and monkey somatosensory cortical neurons, of the direction of stimuli moving across the skin surface. Rats employ subtly different combinations of whisker velocity and amplitude depending on the nature of the textured surfaces they are palpating.

Not surprisingly, the neural mechanisms involved in coordinating the motor and sensory functions of the whiskers are located throughout the brain and involve nearly every major neural center. The whisker system itself is perhaps best viewed as an overlaid system of multiple closed anatomical/functional loops (Kleinfeld et al., 1999). Afferent sensory pathways originate in the whisker hair follicles and terminate in sensory areas of the cerebral cortex. Motor pathways, including those arising from the motor cortex, eventually terminate in the brainstem facial motor nucleus whose motorneurons directly innervate muscles responsible for whisker movement. Linkages between sensory and motor structures at many levels of the pathways provide for integration of sensory and motor processing centers, enabling animals to adjust whisking and sniffing movements based on the ongoing barrage of acquired sensory information.

The complexity of the system notwithstanding, whisking is rapidly emerging as an important model for the study of motor rhythms and sensorimotor integration. The mechanical apparatus itself is relatively simple (Dorfl, 1982). Each whisker follicle is enveloped by a sling of striated muscle that wraps around the base of the follicle rostrally and attaches to the immediately caudal follicle nearer the skin surface (Figure 1). Contraction of the sling muscles pull the base of the follicle backward and, due to the lever-like mechanical coupling of the follicle to the overlying skin, the whisker moves forward, or "protracts." Retraction is more rapid and is thought to reflect largely the viscoelastic properties of mystacial pad tissue. Whisking thus occurs within a single plane (horizontal with respect to the face) and does not involve load-bearing, articulated joints and coordination of complexly organized agonist and antagonist muscle groups. The sling muscles themselves are anatomically and functionally homogeneous, and whiskers on the mystacial pad move in unison with each other and in synchrony with whiskers on the other side of the face. All of these features greatly simplify the measurement and analysis of whisking behavior.

Whisking, like other rhythmic motor acts, has been thought to reflect the operations of small networks of

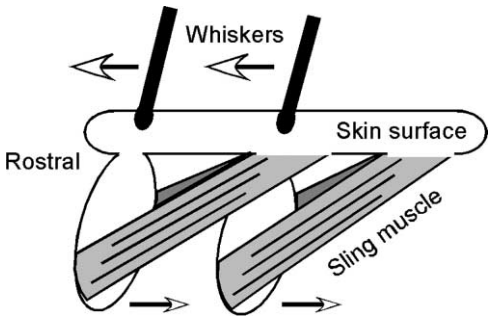

Figure 1. Forward Whisker Movement Produced by Contraction of Sling Muscles

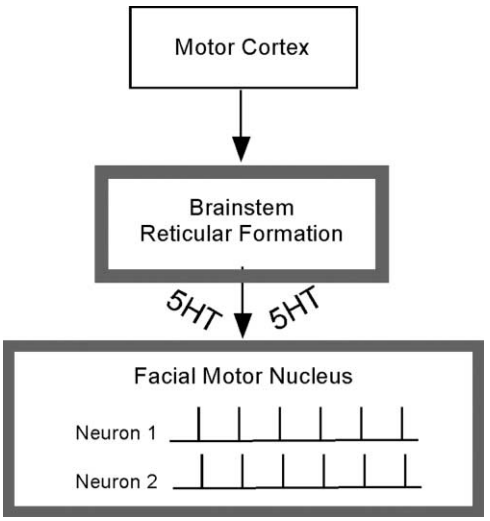

Figure 2. Simplified Schematic of Whisking CPG (Thickly Lined Boxes) and Its Control by Motor Cortex

neurons called "central pattern generators" (CPGs) (Grillner et al., 1998), which produce periodic firing in whisker facial motorneurons (wFMNs). A major impediment in the field has been the lack of identification of the whisking CPG. Whisker motor cortex projects widely to the brainstem but not directly to the facial motor nucleus. Moreover, lesions of motor cortex fail to abolish whisking. These findings suggest that the whisking CPG is located subcortically, likely in the brainstem. Unfortunately, neurons that project to the facial motor nucleus are located in many brainstem nuclei and, in addition, are scattered widely and diffusely throughout the reticular formation (Hattox et al., 2002). Based on earlier studies, Hattox et al. reasoned that serotonin may constitute a key neurotransmitter in the CPG. They used immunohistochemical staining to establish first that neurons in the whisker region of the facial motor nucleus were indeed densely innervated by serotonergic axons. They then placed a retrogradely transported label in the facial motor nucleus and, in the same specimen, an anterograde tracer in the contralateral whisker motor cortex. This enabled the investigators to identify brainstem neurons that both project to the wFMNS and likely receive inputs from motor cortex. Many such neurons, termed "pre-wFMNS," were located in brainstem nuclei that contain the serotonergic neurons which project to the wFMNs.

These anatomical findings strongly suggested that motor cortex indirectly influences whisking by controlling levels of serotonin in the facial motor nucleus. To test this hypothesis, Hattox et al. electrically stimulated regions of the brainstem in anesthetized rats and, in some cases, were able to produce movement of a small number of whiskers, though the movement did not outlast the stimulus and was not rhythmic. Similar effects were produced pharmacologically by injection of a glutamate analog, which enabled the investigators to activate pre-wFMNs while avoiding complications associated with electrical stimuli. Sites of electrical- or chemical-induced whisker movement were located in nuclei identified by the previous immunohistochemical and anatomical studies as containing serotonergic pre-wFMNs.

In order to address more directly the role of serotonin, Hattox et al. next employed a brainstem slice preparation and whole-cell recordings from wFMNs. The cells' biophysical properties and responses to depolarizing current pulses indicated that wFMNs do not intrinsically generate rhythmic burst firing. Bath application of serotonin, however, depolarized the neurons and led to continual periodic firing at 6 Hz, well within the normal range of whisking. Rhythmic firing was evoked by serotonin even in the absence of the excitatory transmitter glutamate and the inhibitory transmitter GABA, and such firing was mediated specifically by two serotonin receptor subtypes. Thus the whisking CPG includes serotonergic neurons in the brainstem reticular formation and the serotonin-sensitive wFMNs in the facial motor nucleus (denoted by thick lines in Figure 2). The precise mechanisms (e.g., voltage-dependent conductances) by which serotonin produces rhythmic activity in wFMNs is, as yet, unexplored. Also unknown and critically important is how activity within populations of wFMNs becomes synchronized, a necessary prerequisite for the uniform movement of multiple whiskers. One possibility suggested by the investigators is that wFMNs are electrically coupled.

If periodic motoneuron firing of wFMNs depends on their activation by serotonin, then whisking should be abolished by blockade of serotonin receptors in the facial motor nucleus. To address this causal relationship, Hattox et al. used an implanted microdialysis probe to apply serotonin receptor antagonists unilaterally onto wFMNs in behaving rats. Because whisking is normally bilaterally symmetric, the movement of the contralateral whiskers could be used as a control condition. Infusion of antagonists of specific serotonin receptors, identified previously in the in vitro experiments, severely altered whisking on the experimental side, reducing the size of whisker protractions and disrupting the rhythmic pattern of the movements.

On the basis of their findings, Hattox et al. propose a relatively simple model of whisking wherein descending cortical inputs excite serotonergic neurons in the brainstem, which in turn release serotonin on wFMNs (Figure 2). This produces rhythmic firing in motoneurons, synchronized perhaps by electrical coupling, whose period

depends on the concentration of released serotonin. Though simple, the model leads to a number of testable hypotheses. For example, it provides a potential mechanism for the cortical control of whisking frequency. Motor cortex neurons are known to fire several tens of milliseconds prior to the start of a whisking epoch (Carvell et al., 1996). According to the Hattox et al. model, higher firing rates and/or engagement by larger numbers of brainstem-projecting motor cortex neurons would evoke greater firing in the pre-wFMNs. This in turn would lead directly to more serotonin release onto wFMNs and, hence, a higher frequency of motorneuron firing and of whisking.

In the dialysis experiments, serotonin antagonists disrupted whisking ipsilaterally but did not completely abolish it. Hattox et al. report the interesting observation that whiskers on the experimental side would often move at the beginning of a several second-long whisking epoch and then remain immobile except for occasional movements, when they would move in synchrony with the ongoing movements of the contralateral whiskers. Together, the findings indicate that though serotonin is essential for rhythmic whisker movements, bilateral synchronization and the initiation of whisking are mediated by other mechanisms. Identification of these coordinating centers, and in particular of the role of motor cortex, are critically important questions for future research. The discovery of the whisking CPG, or at least one of its major components, represents a fundamental advance in our ability to understand the motor that drives the whisk.

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