A central goal of neuroscience is to explain how neural networks generate organized and repetitive motor patterns, such as active whisking used by rodents to navigate the environment. Whisking consists of fast rhythmic ellipsoid vibrissa movements through the air and objects at between 4 and 15 Hz, which are characterized by vibrissa protractions (Berg and Kleinfeld 2003; Carvell and Simons 1990; Carvell et al. 1991; Harvey et al. 2001; Kleinfeld et al. 2006; Welker 1964). Because active whisking does not require sensory feedback (Gao et al. 2001; Welker 1964) or the motor cortex (Carvell et al. 1996; Gao et al., 2003; Semma and Komisaruk 1984), a circuit located in the brain stem is assumed to generate whisking (Hattox et al. 2003).

Similar circuits responsible for generating rhythmic motor patterns for locomotion, respiration, and feeding are called central pattern generators (CPG) (Grillner 2006; Marder et al. 2006; Welker 1964). Because active whisking does not require sensory feedback (Gao et al. 2001; Welker 1964) or the motor cortex (Carvell et al. 1996; Gao et al., 2003; Semma and Komisaruk 1984), a circuit located in the brain stem is assumed to generate whisking (Hattox et al. 2003). The existence of a CPG for whisking raises two obvious questions. First, what are the neuronal elements and the connectivity of the whisking CPG? Second, how does the CPG operate to generate whisking? In a paper published in this issue of the Journal of Neurophysiology (p. 2148–2158), Cramer et al. propose a model that answers these questions.

Using brain stem slices from young rats (P13-18), current- and voltage-clamp recordings were obtained from vibrissa motoneurons (vMNs). Application of a serotonin (5-HT) receptor agonist depolarized the vMNs producing rhythmic trains of action potentials at whisking frequencies (1.5–17 Hz). The firing frequency varied as a function of the concentration of the agonist. Because this effect was not affected by blocking glutamate and GABA receptors, it most likely involves changes in the intrinsic properties of vMNs, such as an enhanced inward current or a suppressed outward current. An obvious candidate is the persistent Na⁺ current (I_{Nap}), which is caused by a small portion of Na⁺ channels that linger in the activated state (Crill 1996). Although, I_{Nap} is small compared with the transient Na⁺ current, it is functionally important because it activates at subthreshold potentials and so can greatly increase the excitability of otherwise quiescent neurons. Accordingly, a role for I_{Nap} in other CPGs has been established (Harris-Warrick 2002).

To determine if persistent inward currents were affected by serotonin (5-HT), slow voltage ramps that inactivate the transient currents were applied in voltage clamp. These ramps revealed a persistent inward current in vMNs that was mostly suppressed by TTX, indicating that it is I_{Nap}. Application of a 5-HT agonist greatly enhanced I_{Nap} and shifted its activation threshold even more negative, thus making vMNs much more excitable in the subthreshold range. Furthermore, in current clamp, riluzole (an I_{Nap} blocker) reversed the effects of a 5-HT agonist on the rhythmic firing of vMNs.

Based on these results, Cramer et al. propose that through the graded facilitation of I_{Nap}, 5-HT can generate the full range of whisking frequencies in vMNs. This implies that the firing rate of serotonergic cells that project to vMNs (5-HT premotor neurons in the lateral paragigantocellularis nucleus) should correlate with the whisking frequency because the concentration of 5-HT in the facial nucleus will determine the firing of vMNs and thus whisking frequency. The authors tested this hypothesis using anesthetized rats in vivo and found that the tonic activity of putative serotonergic premotor neurons indeed correlates with the frequency of whisking triggered by motor cortex stimulation.

The major point of the model that emerges from these results is that vMNs actively participate in the rhythmonogenesis by converting tonic serotonergic inputs into the patterned motor output responsible for movement of the vibrissa (see Fig. 1). In essence, all you need are a few motoneurons and some level of [5-HT]₀ that upregulates I_{Nap} and you have whisking. The beauty of this proposal is without a doubt its simplicity. This simplicity also raises some stimulating questions for future studies.

An apparent requirement for whisking is that vMNs fire in synchrony to coordinate the motor output. How is this synchrony implemented among vMNs during whisking? Unless there is an additional not-yet-identified synchronizing input (e.g., inhibitory), the current model must implement synchrony within the facial nucleus. If such an extrinsic synchronizing input does not exist and because vMNs do not form synaptic collaterals between each other, then the most obvious alternative is that vMNs are synchronized via gap junctions.

The proposed CPG is a feedforward circuit that can operate in the absence of intrinsic feedback circuitry to keep it under control. Then how does the CPG regulate itself? The only evident feedback is extrinsic to the CPG and involves the sensory input returning via the infraorbital nerve through the trigeminal complex (Nguyen and Kleinfeld 2005). Thus this feedback loop probably regulates the output of the CPG. Also, in the current model, only vibrissa protractions are actively controlled, whereas retractions are assumed to occur passively. However, the extrinsic muscles actively control retractions of the whisker pad (Berg and Kleinfeld 2003). Are these muscles and retractions controlled by another CPG? If so, do protrusion and retraction CPGs interact with each other?

In many cells, a variety of neuromodulators can regulate the same ionic conductance. Perhaps, several neurotransmitters can upregulate I_{Nap}. Can other neuromodulators regulate I_{Nap}?
in vMNs and therefore produce whisking? Likewise, inhibition and fast excitation can support oscillatory activities as those required for whisking. Then what are the roles of excitatory inputs from motor cortex onto vMNs (Grinevich et al. 2005) and of the many other vMNs afferents (Hattox et al. 2002) during whisking?

As the authors argue, several different mechanisms and/or circuits may possibly drive whisking. For instance, during abnormal conditions (i.e., disinhibition), the motor cortex can operate as a CPG for whisker movements by generating an intrinsic oscillation at ~10 Hz that drives rhythmic retractions at the same frequency (Castro-Alamancos 2006). Interestingly, the motor cortex CPG also appears to depend on $I_{\text{Nap}}$ (Castro-Alamancos et al. 2006). If the proposed brain stem CPG is one of several circuits responsible for different types of whisking, what coordinates the actions of these multiple CPGs?

It is humbling to realize that the neural generator for such a simple behavior as the repetitive motion of the vibrissa is still unexplained, which underscores the challenge of explaining more complex behaviors. Certainly the work by Cramer et al. takes us closer to that important goal.

REFERENCES


