LETTER TO THE EDITOR

Reply: The cuneiform nucleus may be involved in the regulation of skeletal muscle tone by motor pathway: a virally mediated trans-synaptic tracing study in surgically sympathectomized mice

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Sir, We appreciate the opportunity to respond to the comment by Xiang et al. (2013) on our review on interspecies differences in the pedunculopontine nucleus area. As exemplified by the data of Xiang et al. (2013) it is evident that the mesencephalic locomotor region compromises several distinct structures that are involved in initiation and inhibition of gait, and certainly the implications of both the cuneiform nucleus and the subcuneiform nucleus need to be studied in more detail. Also, as mentioned in our review, there is a paucity of data on the downstream mechanisms mediating neuronal activity in the mesencephalic locomotor region.

The role of the pedunculopontine nucleus area as a target site for deep brain stimulation for treatment of medically refractory gait and postural abnormalities in late stage Parkinson's disease and progressive supranuclear palsy still needs further clarification. Because post-mortem studies in Parkinson's disease and progressive supranuclear palsy show ~60% loss of cholinergic neurons in the pedunculopontine nucleus (Jellinger, 1988) it should also be considered that stimulation of the pedunculopontine nucleus area may involve activation of adjacent structures in the mesencephalic locomotor region, especially the cuneiform nucleus through neuronal modulation of efferents to motor neurons (Milner and Mogensen, 1988). The pedunculopontine nucleus and the cuneiform nucleus are diffusely intermingled and topographically and neurochemically not well defined. Cytoarchitecturally the pedunculopontine nucleus consists of a dorsolateral compact part, the 'pars compacta', with a higher density of cholinergic neurons and a diffuse part, the 'pars dissipata' with glutamatergic, cholinergic and other neuron types, situated at the rostrocaudal axis. The cuneiform nucleus consists of GABAergic and nitricergic neurons (reviewed in Inglis and Winn, 1995; Alam et al., 2011).

Both pedunculopontine nucleus and cuneiform nucleus have been suggested to facilitate muscle tone during the initiation of locomotion (Mori et al., 1987; Alam et al., 2011). Lesion within the pedunculopontine tegmental area pars dissipata in rats resulted in motor deficits, which is consistent with the hypothesis that the anterior pedunculopontine nucleus (the homologue to the pedunculopontine tegmental area pars dissipata in rodents), has functions related primarily to motor control, whereas the posterior pedunculopontine nucleus (the pedunculopontine tegmental area pars compacta) is less involved in motor activity (Alderson et al., 2008). More recent studies, however, have shown that specific lesions of cholinergic neurons in the pedunculopontine tegmental area pars compacta result in motor dysfunction (Aziz and Stein, 1997; Karachi et al., 2010). So far, an anatomical connection between pedunculopontine nucleus and spinal cord has been demonstrated in humans by using diffusion tractography (Muthusamy et al., 2007) but not for the cuneiform nucleus.

Xiang et al. (2013) aimed to elucidate the motor neuronal circuitry between the skeletal muscle and cuneiform nucleus. They found that neurons in the cuneiform nucleus and the caudal pars compacta of the pedunculopontine tegmental area, which were retrograde labelled after injection of the pseudorabies virus in the gastrocnemius muscle, were not double-labelled for tyrosine hydroxylase and serotonin, whereas neurons in the pars dissipata of the pedunculopontine tegmental area were double-labelled.
The authors concluded that neuronal populations in the cuneiform nucleus and caudal pars compacta of the pedunculopontine tegmental area differ from those of the pars dissipata of the pedunculopontine tegmental area, and suggested that the cuneiform nucleus and the caudal pars compacta of the pedunculopontine tegmental area regulate motor pathways by a direct neuronal circuit from the caudal pars compacta of the pedunculopontine tegmental area and cuneiform nucleus to skeletal muscle. Based on these findings the authors propose that neurons within the cuneiform nucleus send projections to the medullary reticular formation, which in turn projects to the central horn motor neurons, which control skeletal muscle tone regulated by both α and γ motor neurons.

Although the findings of Xiang et al. (2013) are certainly of interest, we think that it is premature to suggest the cuneiform nucleus directly as a target for deep brain stimulation in humans. One should also keep in mind that the caudal pars compacta of the pedunculopontine tegmental area and the cuneiform nucleus differ with regard to their predominant neurotransmitters. In Parkinson’s disease or progressive supranuclear palsy the loss of cholinergic neurons in the pedunculopontine tegmental area might be pivotal for disturbances of gait and posture (Warren et al., 2005). Further experiments would be needed to elucidate if and how stimulation of the cuneiform nucleus would affect muscle tone when cholinergic neurons of the pedunculopontine tegmental area are lost. Additionally, with regard to the interspecies differences considered in our review (Alam et al., 2011), the question remains whether the findings shown in mice would also apply to humans. Although the topography and morphological structure are probably similar in most mammals, the distribution of cholinergic, glutamatergic or GABAergic neurons within these regions and the degree of afferent and efferent fibres may vary, which could account for species-dependent outcome of behaviour in experimental settings.

References


