The sacral parasympathetic system is actually sympathetic—and other updates on recent autonomic research

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The sacral autonomic outflow is sympathetic

For at least a century, teachings on the neuroanatomy of the autonomic nervous system have included the doctrine that the sacral outflow is parasympathetic in nature. This doctrine has its foundation in research carried out by W.H. Gaskell and J.N. Langley in the late 1800s and early 1900s and has been circulated in textbooks and neuroanatomy courses ever since. This “craniosacral” outflow model of the parasympathetic system is based on several anatomical and physiological similarities between the outflow of the cranial and sacral autonomic nerves, namely that their target areas are more specific than those of the thoracolumbar sympathetic nerves, that they lack projections to the paravertebral sympathetic chain, and that they are sensitive to muscarinic antagonists. This doctrine has been disputed recently by Espinosa-Medina and colleagues in an article published in the November 2016 issue of *Science* [1].

These authors compared the genetic signature of sacral preganglionic neurons with those of cranial preganglionic neurons (represented by the dorsal motor nucleus of the vagus nerve [DMV]) and thoracolumbar preganglionic sympathetic neurons in the spinal cord of developing rat embryos. Like humans, the sympathetic ganglia of rodents arise from neural crest cells that detach from the neural tube and migrate to their final destinations along the paravertebral chain, cervical chain, and organ plexuses. In contrast, parasympathetic ganglia arise from glial-like

preganglionic nerve fibers that serve as a bridge for migrating precursor cells. Espinosa-Medina and colleagues found that lesioning the sacral splanchnic nerves did not impair the formation of pelvic ganglia, providing support to the notion that the formation of the sacral ganglia is migratory and nerve-independent, similar to the formation of sympathetic ganglia.

In their publication, Espinosa-Medina et al. [1] also reported that various transcription factors in the sacral preganglionic neurons were indistinguishable from those of the thoracolumbar neurons, and much different from those found in the DMV. This transcription factor “fingerprint” lends further support to the notion that the sacral outflow is sympathetic from development. Overall, this study provides an example of how modern molecular biology techniques can turn ancient paradigms on their head (or tail, in this case), leading to the old system of “craniosacral outflow” being discarded for a new paradigm of distinctly separate cranial and spinal outflow systems. This new paradigm sheds new light on the autonomic response of the sexual organs and may provide an avenue for new therapeutics for patients with pelvic autonomic impairment.

Intraoperative baroreceptor stimulation during endarterectomy

Patients with baroreflex failure represent a challenge to clinicians. Etiologies of baroreflex failure may include carotid artery stenosis, carotid body tumors, surgical damage to the glossopharyngeal nerve, and neck irradiation [2, 3]. Work carried out by A. Carlsten, A.M. Bilgutay, and E. Braunwald and their colleagues in the 1950s and 1960s demonstrated that electrical stimulation of the carotid sinus results in the reduction of both blood pressure and heart

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rate. More recently, baroreflex stimulator devices have shown promise in early trials as a means to reduce blood pressure in patients with refractory hypertension [4].

In a study published in the December 2016 issue of *Autonomic Neuroscience: Basic and Clinical* [5], Kansal and colleagues conducted a detailed mapping of blood pressure and heart rate responses to stimulation of various areas within the carotid sinus in ten patients undergoing carotid endarterectomy (CEA) for atheromatous plaque removal. The degree of carotid stenosis in these patients ranged from 70 to 90%, and all patients were evaluated during CEA, while under general anesthesia with mechanical ventilation. Seven patients received a combination of propofol and nitrous oxide, and three patients received sevoflurane. Nine of the patients also received a phenylephrine infusion to stabilize blood pressure at some point during the procedure. Stimulator electrodes were placed in the region of the carotid sinus and held in place against the vessel wall, and a neural stimulator was used to deliver bipolar pulses at various sites. After CEA and -plaque removal, blood pressure was allowed to stabilize and the stimulation protocol was repeated.

The most robust hypotensive response occurred with stimulation of the medial wall of the internal carotid artery with longitudinally placed electrodes. Prior immunohistochemical studies had revealed that this region of the carotid artery is particularly dense in baroreceptors [6]. When stimulated, systolic blood pressure and heart rate changed by -12.3 ± 6.9 mmHg ($p < 0.001$) and -3.7 ± 5.2 bpm ($p < 0.05$), respectively. It is important to note that all measurements were taken while the subjects were anesthetized, thus the blood pressure response might have been blunted. There were no differences in pre- versus post-CEA blood pressure responses to stimulation, however spontaneous baroreflex sensitivity was greater post-CEA.

This study provides valuable insight on baroreflex anatomy, adding to the growing body of literature on procedural techniques that may be used in the future for refractory patients with baroreceptor failure who do not respond to oral medications.

Imaging autonomic dysfunction in Parkinson disease

Autonomic failure is common in Parkinson disease (PD). It has been suggested that the degeneration of brainstem nuclei, observed in postmortem studies, is one of the pathological bases for this debilitating non-motor feature. In clinical practice, autonomic dysfunction is quantified by tests of cardiac sympathetic and vagal function. However, it is unclear whether brainstem pathology correlates with

the degree of autonomic dysfunction. A recent study conducted by Pyatigorskaya and colleagues, published in the December 2016 issue of *Neurology* [7], had the aim to identify and correlate brainstem imaging findings on diffusion tensor imaging with heart rate variability during sleep. In this case-control study, these researchers identified 52 patients with PD and 24 healthy controls, all of whom underwent diffusion tensor imaging studies. In addition, both the PD patients and healthy controls had their heart rate and respiratory variability measured during rapid eye movement (REM) and slow wave sleep. To ensure that the diffusion tensor imaging findings were truly reflective of focal autonomic nuclei pathology—and not a marker of global disease—the researchers also imaged the hippocampus. The results showed that the PD patients had a higher axial, mean, and radial diffusivity in the posterior medulla when compared to the controls. In addition, there was a significant correlation between decreased heart rate variability and respiratory variability during REM sleep and a higher mean diffusivity in the medulla of PD patients; similar changes were not noted during slow wave sleep.

There was no correlation between diffusion imaging changes and the duration or severity of PD motor manifestations. It is likely that the changes in medullary regions visualized on diffusion tensor imaging are truly reflective of autonomic dysfunction in PD and that this finding provides a unique and specific imaging marker to identify and assess the progression of autonomic failure in PD.

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