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Highlights in basic autonomic neuroscience: Semaphorins in the remodeling of autonomic innervation

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ABSTRACT

Chemorepellent signals of the semaphorin family are known to play a crucial role in the development of the nervous system. Some semaphorins continue being expressed in the adult life when they regulate plasticity and regeneration. Increasing evidence indicates that semaphorins are implicated in the development of the autonomic nervous system as well as in the regulation of different forms of plasticity observed in the adulthood. Here we present selected examples illustrating the involvement of semaphorins in the regulation of autonomic plasticity in physiological and pathological conditions.

Introduction

Semaphorins are a family of proteins that were discovered in the early 1990s and originally identified as cues that guide axons through repulsion during the development of the nervous system. It is now clear that semaphorins are repeatedly used throughout development and reused in postnatal and adult life, controlling plasticity and regeneration (Pasterkamp, 2012). To date, more than twenty semaphorins of secreted or membrane forms have been identified and categorized into eight classes (Semaphorin Nomenclature Committee, 1999). Here we present advances in semaphorin research focusing on autonomic nervous system and highlight semaphorin implications in both physiological and pathological aspects of neuronal plasticity.

Ieda, M., Kanazawa, H., Kimura, K., Hattori, F., Ieda, Y., Taniguchi, M., Lee, J-K., Matsumura, K., Tomita, Y., Miyoshi, S., Shimoda, K., Makino, S., Sano, M., Kodama, I., Ogawa, S., Fukuda, K. (2007). Sema3a maintains normal heart rhythm through sympathetic innervation patterning. Nature Med. 13, 604–612.

Article summary

Cardiac tissues are extensively innervated by sympathetic nerves. In the ventricle, sympathetic nerves distribute predominantly in the subepicardium and this epicardial-to-endocardial transmural innervation gradient is crucial for effective cardiac performance. In this study, the authors showed that during development, semaphorin 3A (*Sema3a*) is produced by cardiomyocytes and demonstrated that this chemorepellent signal contributes to the establishment of the organotypic sympathetic innervation. *Sema3a* homozygous null mice ($Sema3a^{-/-}$) showed a marked reduction in the subpericardial-to-subendocardial ratio of sympathetic innervation. Moreover, $Sema3a^{-/-}$ mice showed stellate ganglia malformation, which led to sinus bradycardia due to sympathetic dysfunction. Cardiac-specific overexpression of *Sema3a* in transgenic mice (*SemaTG*) elicited reductions in sympathetic innervation and an attenuation in the epicardial-to-endocardial sympathetic innervation density. *SemaTG* mice showed sudden death and increased susceptibility to ventricular tachycardia due to catecholamine supersensitivity and prolongation of action potential duration.

Commentary

The organotypic pattern of distribution and relative density of sympathetic nerves in the heart are critical for normal cardiac function. There is evidence that cardiac innervation is altered in pathological hearts, such as following myocardial infarction. In spite of its clinical relevance, factors determining cardiac innervation are not fully understood. Neurotrophic factors from the neurotrophin and glial cell line-derived factor families are known to be critical chemoattractants for cardiac sympathetic nerves (Kimura et al., 2012). In particular, heart levels of nerve growth factor (NGF) correlate with the density of sympathetic innervation and NGF upregulation in the infarcted myocardium elicits sympathetic sprouting and heterogeneous innervation (Ieda and Fukuda, 2009). The participation of chemorepellent molecules in the development and maintenance of normal cardiac innervation was not investigated until recently. Sema3a, the prototypic member of the class 3 secreted semaphorins, has been shown to be a potent chemorepellent for sympathetic axons. In this work, Ieda and colleagues demonstrated that appropriate expression of Sema3a in cardiac tissue is needed for the patterning of sympathetic nerves and is critical for heart rate control. Their work also showed a negative correlation between the pattern and kinetics of Sema3a expression and the distribution and density of sympathetic innervation in the developing heart, indicating that Sema3a negatively

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regulates cardiac innervation. In this context, current evidence indicates that the balance between NGF and Sema3a synthesized by the cardiac tissue determines heart sympathetic innervation. Consistently, alterations in Sema3a expression disrupt cardiac innervation patterning and lead to sudden cardiac death and lethal arrhythmias. In line with this concept, a recent study (Wen et al., 2011) presented evidence indicating that Sema3a attenuates electrical remodeling at the infarct border zones in a rat model of myocardial infarction. Similarly, it has been suggested that increased expression of Sema3a may partially account for the sympathetic denervation observed in congestive heart failure (Sun et al., 2011). Taken together, these results indicate that Sema3a plays a crucial role in the development of cardiac sympathetic innervation and would be involved in heart diseases, thus making this molecular signal a potential target for pharmacological interventions.

Straub, R.H., Lowin, T., Klatt, S., Wolff, C., Rauch, L. (2011). Increased density of sympathetic nerve fibers inmetabolically activated fat tissue surrounding human synovium and mouse lymph nodes in arthritis. Arthritis & Rheumatism 63, 3234–3242.

Article summary

In previous studies, Straub's group demonstrated that members of the Class 3 secreted semaphorins are involved in the loss of sympathetic nerve fibers in inflammatory lesions. In this study, they looked for changes in the density of sympathetic nerve fibers in the fat tissue surrounding inflamed regions. This article demonstrated increased density of sympathetic nerve fibers in fat tissue adjacent to human synovium of arthritic patients and in adipose depots around the lymph nodes of mice with experimental arthritis. The authors interpreted that sympathetically induced local activation of lipolysis may provide the energy-rich fuels (fatty acids) that are necessary to nourish the neighboring inflammatory process. In addition, they speculated that semaphorin-induced repulsion of sympathetic nerve fibers from inflamed regions might contribute to the increased occurrence of these nerves in the adjacent fat tissue.

Commentary

The loss of sympathetic nerve fibers is a general principle in inflammation. It has been suggested that loss of sympathetic nerve fibers from inflamed lesions is an evolutionarily conserved mechanism allowing an adequate immune/inflammatory response which would be prevented in the presence of these nerves (Straub and Besedovsky, 2003). Although the loss of peripheral nerve fibers in inflamed areas has been described for many years, the role of nerve repellent factors in inflammatory diseases has recently begun to be investigated. Straub and colleagues recently demonstrated the concept of intentional repulsion of sympathetic nerve fibers by semaphorins. In particular, semaphorin 3F (Sema3F) was shown to be a strong repellent for sympathetic nerve fibers leading to rapid repulsion within hours. Moreover, there is evidence indicating that Sema3F is upregulated in the synovial fibroblasts and macrophages present in inflamed tissue of arthritic patients (Fassold et al., 2009). The question appears as to what is the stimulus for the increase of nerve fibers in the fat tissue surrounding inflamed lesions reported in this study. Although there is no direct proof that upregulation of repellent factors in inflamed tissue is the cause of an increased number of nerve fibers in the adjacent fat tissue, the authors interpreted this coincidence as an adaptive program induced by semaphorins expressed in inflamed tissue. Considering that the sympathetic nervous system should serve the activated immune system, this semaphorin-induced compartmentalization of nerve fibers (present in the fat tissue but not in inflamed tissue) could allow parallel lipolysis and immune activation, solving the two contrasting functions of adrenergic neurotransmitters in favor of a proinflammatory milieu.

Richeri, A., Chalar, C., Martínez, G., Grief, G., Bianchimano, P., Brauer, M.M. (2011). Estrogen up-regulation of semaphorin 3F correlates with sympathetic denervation of the rat uterus. Auton. Neurosci.: Basic Clinic 164, 43-50.

Article summary

The sympathetic innervation of the uterus is remarkably dynamic and undergoes considerable remodeling in response to physiological and experimental changes in systemic levels of sex hormones. In particular, estrogen inhibits the growth and causes the degeneration of intrauterine sympathetic nerve fibers in the non-pregnant female. In this article, the authors evaluated whether semaphorin 3F (Sema3F), a potent sympathetic nerve repellent, was produced by the rat uterus and if its expression was modulated by estrogen. These studies showed that chronic exposure to estrogen of immature rats led to a 5-fold induction of Sema3F mRNA. In situ hybridization revealed that Sema3F transcripts were distributed in the myometrial connective tissue and selectively expressed by fibroblasts and infiltrating eosinophil leukocytes. Immunohistochemistry showed that some isolated axonal profiles present in the estrogenized uterus were immunoreactive for the Sema3F binding receptor, neuropilin-2.

Commentary

Regulation of estrogen-induced remodeling of uterine innervation involves changes in the ability of myometrium to support its sympathetic innervation. After failing in demonstrating reductions in neurotrophic support (Brauer, 2008), investigations were addressed to disclose the potential contribution of inhibitory signals for sympathetic nerves. Studies developed in the last decade have shown that, under the influence of estrogen, the myometrium produces a range of target-derived molecular signals with negative effects on sympathetic nerves, including brain-derived neurotrophic factor and neurotrimin (Krizsan-Agbas et al., 2003, 2008). The study by Richeri and co-workers provided the first evidences indicating a positive correlation between the pattern and kinetics of sema3F expression and the estrogen-induced degeneration of myometrial sympathetic nerves. Although correlative in nature, these results suggest that Sema3F negatively regulates uterine innervation in response to estrogen. Similarly, an increased immunostaining for Sema3A has been demonstrated in the human myometrium during pregnancy (Marzioni et al., 2004). These results suggest that under certain hormonal conditions, the uterus may produce several semaphorins with potentially redundant negative effects for sympathetic nerves. Two main cell types appeared to be responsible for the sema3F expression observed in estrogen-treated animals: fibroblasts and eosinophil leukocytes. This is not surprising because in other models, semaphorins are produced by a wide range of cells, including fibroblasts and inflammatory cells. Finally, this article describes the presence of axon profiles positive for neuropilin 2, the binding receptor for Sema3F, thus giving additional support to the hypothesis that Sema3F is involved in the degeneration elicited by estrogen in uterine sympathetic nerves.

Naska, S., Lin, D.C., Miller, F.D., Kaplan, D.R. (2010). p75NTR is an obligate signaling receptor required for cues that cause sympathetic neuron growth collapse. Mol. Cel. Neurosci. 45, 108–120.