BACKGROUND:
It is well recognized that the sympathetic nervous system modulates inflammatory and immune responses. In particular, adrenomedullary catecholamines play an important role in this sympathetic immunomodulatory system. Because sympathetic preganglionic neurons (SPNs) directly innervate the adrenal medulla, it is plausible that increase of SPNs activity through other neuronal circuits subsequently release adrenal medullary catecholamines leading to the anti-inflammation. However, it is not well documented that specific spinal neuronal mechanisms related to these SPNs activity that modify peripheral inflammation.

PURPOSE:
This study was designed to evaluate following subjects:
1. It has been reported that increase of spinal cholinergic activity activates SPNs. Based on this premise we hypothesized that an increase of spinal cholinergic activity would produce an anti-inflammatory effect and that this effect would be mediated by activation of the sympatho-adrenomedullary system.
2. It has been established that SPNs are modulated by GABAergic inhibitory input. Therefore, it was examined whether spinal cholinergic activity is associated with this spinal GABAergic pathway leading to anti-inflammation.
3. Since a number of studies have previously shown that spinal β2-adrenoceptors are functionally associated with spinal cholinergic activity, we next examined whether spinal cholinergic receptors were also related with these β2-adrenoceptors in the anti-inflammatory mechanism.
4. Peripheral bee venom (BV) stimulation activates descending noradrenergic system through increase of activity of brain catecholaminergic nucleus including locus coeruleus (LC, major descending noradrenergic source). In light of this, we hypothesized that BV stimulation-induced LC activation turned on spinal neuronal circuits via descending noradrenergic system and subsequently increased SPNs activity leading to anti-inflammation.

MATERIALS AND METHODS:
In order to evaluate the immune-modulatory role of spinal neuronal circuits related to the SPNs activity, zymosan-induced mouse air pouch model was utilized. In this air pouch model, intrathecal (IT) injections were performed to evaluate the modulatory role of various spinal neurons (cholinergic, noradrenergic or GABAergic neurons) in the peripheral inflammation. Additionally, Fos (neuronal activation marker) and ChAT double-immunohistochemistry was used for examination of the neuronal activation of SPNs.

RESULTS:
1. IT treatment of cholinomimetic drug, neostigmine, significantly suppressed zymosan-induced leukocyte migration in the air pouch. This neostigmine-induced anti-inflammatory effect was blocked by muscarinic type 2 (M2) receptor antagonist, methoctramine. Moreover, this neostigmine-induced anti-inflammatory effect was blocked by adrenalectomy or β-adrenergic antagonist, propranolol.
2. IT injection of M2 receptor agonist, arecaidine but-2-ynyl ester tosylate (ABET) dose dependently suppressed inflammatory response and increased Fos (neuronal activation marker) expression in SPNs of the T7-T11 spinal cord segments (which mainly project to the adrenal medulla). These ABET’s effects were completely blocked by IT pretreatment with GABAB receptor agonist, baclofen. Moreover, IT injection of GABAB receptor antagonist, saclofen significantly reduced leukocyte migration in a dose dependent manner and selectively increased Fos expression in T7-T11 SPNs similar to that of ABET. More importantly, this IT saclofen-induced anti-inflammatory effect was completely blocked by either adrenalectomy or propranolol.
3. IT injection of the β2-adrenoceptor agonist, clonidine produced anti-inflammatory effect and increased Fos expression in T7-T11 SPNs. This clonidine’s effect was reversed by IT pretreatment of methoctramine, adrenalectomy or propranolol.
4. Subcutaneous BV injection into left hind limb showed a marked anti-
inflammation and specifically increased Fos expression in SPNs of the T7-T11. However, contralateral but not ipsilateral lesion of LC by microinjection of 6-hydroxydopamine (selective catecholaminergic neurotoxin) significantly reversed BV-induced anti-inflammatory effect (BVAI). Furthermore, IT administration of ?2-adrenoceptor antagonist or muscarinic M2 receptor antagonist blocked the BVAI. Additionally, contralateral LC lesion or IT methoctramine significantly reduced BV-induced Fos expression in SPNs.

CONCLUSIONS:
Collectively, these results suggested that the activation of spinal noradrenergic ?2-adrenoceptor induced activation of cholinergic M2 receptors leading to a disinhibition of GABAAergic synaptic input onto SPNs, resulting in a suppression of the zymosan-induced inflammatory response via increased release of adrenomedullary catecholamines. Moreover, it was also proposed that BV-induced activation of endogenous descending noradrenergic system produced anti-inflammation via previously described spinal neuronal circuits. Thus the present study provides additional clarification of the spinal cord neurochemical circuitry that underlies the central nervous system's ability to modulate peripheral inflammation.

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