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Regular Article

Transient attenuation of neuropathic manifestations in rats following lesion or reversible block of the lateral thalamic somatosensory nuclei

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Abstract

Background and aims: Nociceptive behavior in animal models for mononeuropathy has been shown to be altered by spinal tract lesions which suggest a possible supraspinal modulation. The thalamus constitutes a chief center for the processing of nociception. We have, therefore, investigated the effects of transient or permanent blocks of the lateral somatosensory thalamic nuclei (the ventrobasal complex) on the neuropathic manifestations in rats.
Methods: Different groups of rats (n = 5–6) were subjected to mononeuropathy, following the spared nerve injury model, known to produce sustained heat hyperalgesia and tactile and cold allodynia which peaked about 2 weeks after nerve injury. This was followed by stereotaxic placement of either electrolytic or chemical lesions or implantation of mini osmotic pump for slow release of lidocaine in the ventrobasal complex.
Results: Chronic electrolytic and chemical lesions or reversible block of the lateral somatosensory thalamus produced transient (1–2 weeks) attenuation of neuropathic manifestations along with a persistent decrease of the hot plate latency. The most pronounced effect was observed on heat hyperalgesia, and the least significant and short-lived effect was observed on cold allodynia.
Conclusion: We conclude that the lateral somatosensory thalamic complex is involved in the processing of neuropathic manifestations but cannot be considered as an obligatory or exclusive relay center for the neuropathic syndromes.

Keywords: Central pain; Pain pathways; Allodynia; Hyperalgesia; Thalamic syndrome

Introduction

The thalamus has been considered to play an ambivalent role in nociception. Traditionally considered as a chief center for pain perception (Head and Holmes, 1911), lesions to the somatosensory thalamic nuclei have been associated with loss of somatosensory functions, including analgesia and anesthesia, on the contralateral side of the body. This loss, however, has been associated with either spontaneous pain referred to the anesthetized areas or with hyperpathia or allodynia observed in that part of the body. These manifestations have been labeled as thalamic syndrome (Dejerine and Roussy, 1906) that has become part of a wider concept of central pain (reviewed by Garcin, 1968; Nashold, 1974; Tasker et al., 1991; Jeanmonod et al., 1994; Bowsher, 1996).

On the other hand, several reports have shown changes in the electrical behavior of thalamic neurons following injuries to either peripheral nerves (Guilbaud et al., 1990; Rinaldi et al., 1991; Rasmusson, 1996; Kaas et al., 1997) or ascending tracts (Hirayama et al., 1989; Lenz et al., 1987, 1989; Radhakrishnan et al., 1999; Miki et al., 2000; Gerke et al., 2003) and during chronic inflammation (Guilbaud et al., 1986).

Abbreviations: AP, anteroposterior; HP, hot plate; IbA, ibotenic acid; KA, kainic acid; L, lateral; PWD, paw withdrawal duration; PWL, paw withdrawal latency; SNI, spared nerve injury; VPL, ventral posterior–lateral; VF, Von Frey filaments.

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In both situations of central or peripheral lesions or injuries, increased nociception (hyperalgesia), disturbed sensations (dysesthesia) and abnormal noxious signaling of non-noxious stimuli (allodynia) are observed. The various interpretations of neuropathic pain led to the concept of an ultimate defect in the processing of nociception at thalamic level. These include one or more of the following: imbalance of the thalamic input, irritation and/or disinhibition of thalamic neurons and imbalance between the lateral and the medial thalamic nuclear systems (Head and Holmes, 1911; Agnew et al., 1983; Cesaro et al., 1991; Tasker et al., 1991; Jensen and Lenz, 1995; Greenspan et al., 2004). Therefore, it becomes necessary to investigate the individual role of the thalamic inputs and thalamic nuclei involved in the processing of somatosensory information.

During the last decade, various animal models have been proposed to simulate neuropathic pain (Bennett, 1994; Ralston, 1998). The neuropathic manifestations observed have been attributed to a complex mixture of transient or persistent changes at peripheral and/or central levels. These include abnormal firing of lesioned and intact sensory fibers and changes in their ionic channels and receptors (Devor and Seltzer, 1999; Waxman et al., 1999), central sensitization and disinhibition (Gracely et al., 1992; Coderre et al., 1993; Cervero and Laird, 1996; Wall, 1991) and sprouting at peripheral and central levels (McMahon and Kett-White, 1991; Woolf et al., 1995). Other recent reports have pointed out the role of supraspinal centers, including brainstem and cerebral structures, in the modulation of neuropathic behavior (Sung et al., 1998; Urban and Gebhart, 1999; Baliki et al., 2003). However, the contribution of the thalamus to the neuropathic behavior in the described animal models has not been fully addressed.

Using the rat model of spared nerve injury (SNI), the present study reports on the effects on neuropathic manifestations of reversible and permanent blocks of the lateral thalamic somatosensory nuclei.

Methods

All experiments were performed on adult Sprague–Dawley rats of either sex with an average weight, at the beginning, of 290 ± 10 g. Rats were housed as groups, 6 animals of the same sex, in large plastic cages under standard colony conditions (12-h light/dark cycle, 23 ± 2°C, free access to food and water). All surgical procedures were performed under deep anesthesia made of atropine (0.05 mg/kg, i.p.) and chlorpromazine (8 mg/kg, i.p.) injected i.p. as preanesthetic and followed, 10 min later, by the injection of ketamine (40 mg/kg, in 0.2 ml, i.p.). The experimental protocol was approved by the Institutional Review Committee for Animal Care, and all procedures were carried with strict adherence to the guidelines for pain investigation in conscious animals (Zimmermann, 1983).

Experimental protocol

This study is based on the results obtained from five groups (n = 5–6 each) of rats. All were subjected to SNI mononeuropathy in their left legs followed 2 weeks later by one of the following treatments: (1) chemical ablation of the ventrobasal neurons using either kainic acid (KA) (n = 6) or ibotenic acid (IbA) (n = 6) injections; (2) electrolytic lesion placed in the ventral posterior–lateral (VPL) nucleus (n = 6); (3) microperfusion of the ventrobasal complex with 2% lidocaine, for a period of 14 days (n = 5); (4) sham group (n = 6) subjected to mononeuropathy, skull surgery and cannula implantation but without injection or lesion in the thalamus.

During the observation period, rats were housed under the same colony conditions and were subjected to two or three sessions of testing per week.

Induction of neuropathy and behavioral testing

Under deep anesthesia, the peroneal and tibial components of the sciatic nerve of the left leg were isolated and cut, leaving intact the sural nerve (Decosterd and Woolf, 2000). The wound was closed and sutured in layers, and each animal received an i.p. injection of penicillin (1 million IU) as prophylactic treatment for 2 consecutive days.

A battery of four behavioral tests was used to assess tactile and cold allodynia and heat hyperalgesia which are considered as indicators of neuropathic manifestations. Detailed description of the procedures used has been previously reported (Saadé et al., 2002; El-Khoury et al., 2002).

Von Frey filaments (VF) of two calibers (2.041 g = 18.5 mN and 11.749 g = 106.7 mN) were used for the assessment of mechanical allodynia with the strength of the largest one considered below the nociceptive threshold in control rats. The acetone drop test described by Choi et al. (1994) was used for the assessment of cold allodynia. For both tests, rats were placed in individual compartment of a cage with a floor made of wire grid allowing free access for stimulation with VF hairs, acetone or radiant heat. Each VF hair was applied to the lateral aspect of the plantar surface of the hindpaws with a force just enough to bend it. This procedure was repeated 10 times on each paw with an average interval of 15–20 s between consecutive applications, and the number of paw withdrawals was recorded. For the cold allodynia, an insulin syringe was used to drop a volume of 25–50 μl of acetone solution on the lateral aspect of each paw. The time of withdrawal reaction of the paw was measured. This time was 0 to 1 s for normal paw and increased in neuropathic paws, and an upper limit of 20 s was assigned as a maximum duration of the reaction (see Saadé et al., 2002).

Two different tests were used for the assessment of heat hyperalgesia: the paw irradiation with a nociceptive heat spot (Hargreaves et al., 1988) and the hot plate (HP) test. Rats were placed in the same elevated cage for the paw irradiation test, and the time to withdraw and the duration of withdrawal were measured as the paw withdrawal latency (PWL) and duration (PWD), respectively. For the HP test, each rat was placed on a heated metal plate (51.2 ± 0.3°C), and the time for paw licking or jumping was monitored as the HP latency in seconds.

Administration of the tests was made randomly during each behavioral test session. One trial per session was made for the HP test. For the acetone drop test, one trial was made on each paw with a minimum interval of 3 min. The application of