Neurons in the Human Thalamic Somatosensory Nucleus (Ventralis Caudalis) Respond to Innocuous Cool and Mechanical Stimuli

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INTRODUCTION

The role of the human principal sensory nucleus (ventralis caudalis, Vc) (see Hirai and Jones 1989) in mediating the sensation of cold is uncertain. Studies in anesthetized squirrel monkeys demonstrate neurons in the corresponding somatosensory nucleus (ventral posterior, VP) (see Hirai and Jones 1989) that respond to both innocuous mechanical and cold stimuli (mechanical-cool neurons) (Burton et al. 1970). Neurons responding to noxious heat and innocuous cold are found within the posterior inferior aspect of human Vc (Lenz et al. 1993b). We now report a new population of cold responsive neurons in human Vc that may contribute to the CNS mechanism mediating the perception of cold in man.

METHODS

The psychophysical, operative, recording, stimulation, and analytic techniques during awake, thalamic stereotactic procedures for treatment of movement disorders and chronic pain have been described previously (Lenz et al. 1988, 1993b, 1994). For patients with movement disorders, sensory function was studied during periods when involuntary movements were absent. This report excluded neuronal activity recorded from regions of Vc that represented the parts of the body where the chronic pain patients experienced sensory abnormalities or chronic pain.

As the electrode was advanced, search stimuli were applied including stroking, brisk tapping, and pinching of the contralateral face and hand, and of parts of the body in the projected field (PF) for microstimulation at adjacent sites. Some neurons with receptive fields (RFs) to cutaneous stimuli (large and small filled circles in Fig. 2B) were studied by application of the mechanical-thermal series of sensory stimuli; other neurons with RFs (open squares) and all neurons without RFs (dots) were not studied with this series. Each sensory stimulus in the series was applied close to the center of the RF with minimal overlap between the areas stimulated by the different modalities. A foot pedal was used to time the application of the mechanical stimuli. Mechanical stimuli in the series included a camel hair brush plus large, medium, and small arterial clips (Lenz et al. 1994). A Peltier device (Wilcox and Geisler 1984) was used to deliver thermal stimuli from a base temperature of 33°C. Postoperatively, action potentials from thalamic single neurons were isolated and analyzed as previously described (Lenz et al. 1994).

RESULTS

We now report results recorded in Vc that was defined as the region where the majority of neurons responded to innocuous cutaneous stimuli. Thermal and mechanical stimuli were applied during recordings from 87 neurons (24 trajectories) in 14 patients with movement disorders or chronic pain. The activity of a single neuron responding to innocuous mechanical and cold stimuli is shown in Fig. 1.

During preoperative sensory testing in the perioral region, the patient described brush (Fig. 1B) as a natural, nonpainful, surface, touch, movement sensation (Lenz et al. 1993a), whereas the large arterial clip was a natural, surface, nonpainful, pressure sensation and the medium clip was a natural, surface, painful, and squeeze sensation, rated at 1 out of 10 on the visual analog scale of pain (VAS). The Peltier probe at 42°C (Fig. 1D) was described as a natural, surface, nonpainful, warm, pressure sensation, whereas the probe at 51°C was described as a natural, surface, painful, and hot sensation (4/10 VAS) and at both 24 and 18°C as natural, surface, nonpainful, cold, pressure sensations.

There was a clear increase in firing rate of the neuron to brushing and to the large but not the medium clip (Fig. 1B). The skin was too thick for application of the small clip. An increase in firing rate was observed during innocuous cooling from 33°C to both 24 and 18°C (Fig. 1C) but not during innocuous or painful heating (Fig. 1D). The response to any stimulus was defined as the firing rate (mean ± SE) calculated across bins over the interval during which the foot pedal was depressed or the temperature was different from baseline.

A one-way analysis of variance (ANOVA) found significant differences in the firing rates measured between baseline and the responses to each mechanical and thermal stimulus (F = 53.3, df = 11, P < 0.00001). Post hoc testing revealed significant (P < 0.00003, Neuman-Keuls test) increases from baseline in response to brushing, application of the large clip, and cooling to 24 and 18°C. The stimulus-response functions for firing of this neuron showed complex patterns for the brush stimulus (Fig. 2A) and other mechanical-cool cells in response to cooling were sig-
FIG. 1. Activity of a neuron in ventralis caudalis (Vc) responding to innocuous mechanical and cold stimuli. A: shape of action potentials discriminated during the cold stimulus plus the receptive field (RF) and projected field (PF) of the neuron. B: response of the neuron to the series of somatic stimuli (as labeled). Bottom trace in each panel of B is the signal from a footswitch indicating the onset and duration of the stimulus. C and D: neuronal response to cold and hot stimuli, respectively. The temperature of the thermode in the Peltier device is shown below the response to each temperature stimulus. The timescales for the histograms are indicated in each panel; all binwidths are 100 ms. The tics along the vertical axes of the histograms are at intervals of 2 counts/100 ms bin.

Figure 2B shows the locations of this (asterisk) and four other neurons with similar response patterns. Nonpainful, tingling sensations overlapping the RF of the neuron were evoked by stimulation (thresholds, 5–30 μA) at all recording sites. The sensation of cold was not reported.

**DISCUSSION**

In this report we describe neurons in human Vc that respond to both innocuous cold and mechanical stimuli but do not respond to painful heat or mechanical stimuli. The presence of neurons in human Vc that respond to innocuous mechanical and cold stimuli is consistent with reports in awake (Bushnell et al. 1993) and anesthetized monkeys (Apkarian and Shi 1994; Burton et al. 1970; Poulos and Benjamin 1968). In the former study a phasic response to cooling was reported for five neurons in dorsal aspect of medial VP (Bushnell et al. 1993) consistent with the present report (Fig. 2). In anesthetized squirrel monkeys 50% of neurons in VP showed a phasic response to cold stimuli (Poulos and Benjamin 1968). These neurons were distributed in somatotopically appropriate parts of VP.

Neurons in human Vc responding to cold stimuli could receive inputs from type 1 slowly adapting mechanoreceptors (Burton et al. 1972; Duclaux and Kenshalo 1972; Hensel and Zotterman 1951; Iggo and Muir 1969) transmitted to thalamus through the dorsal column nuclei (Willis and Coggeshall 1991; cf. Burton et al. 1970). The tonic response of human thalamic neurons to cold stimuli (Fig. 1C) is unlike that of slowly adapting mechanoreceptors, which have a dynamic response to cold stimuli (Burton et al. 1972; Iggo
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trovsky and Craig 1996; Ferrington et al. 1987) to thalamus via the spinothalamic tract (STT) or spinal trigeminothalamic tract (Apkarian and Hodge 1989a,b; Craig 1990; Craig et al. 1994; Kumazawa et al. 1975). This STT projection terminates (Burton et al. 1970) in VP (Apkarian and Hodge 1989b; Ferrington et al. 1987) and in the posterior segment of ventral medial nucleus (Vmpo) (see Craig et al. 1994; Dostrovsky and Craig 1996). Cool fibers respond to cooling with a tonic response like that observed in mechanical-cool cells (see Darian-Smith et al. 1973) (see also Fig. 1C). Cool fibers also respond to warming with a decrease in firing rate (Iggo 1969), like the subtle inhibition observed to heat stimuli in Fig. 1D. Although Aδ cool fibers do not respond to mechanical stimuli, the response of mechanical-cool neurons to mechanical stimuli (Fig. 1B) could be explained by convergence oflemniscal and STT inputs at the level of the thalamus (Pollin and Albe-Fessard 1979). In summary, the responses of thalamic mechanical-cool cells to thermal stimuli are most consistent with Aδ cool fiber input to Vc through the STT cells in the superficial dorsal horn.

Several lines of evidence suggest that the primate principal sensory nucleus is involved in mediating the sensation of cold. Neurons in VP of awake monkeys respond to cooling steps small enough (2°C) to explain the monkeys’ ability to discriminate cold (Bushnell et al. 1993). Injection of lidocaine into VP blocks cold discrimination (Duncan et al. 1993). The polymodal responses of these and other cold responsive neurons in human Vc (Lenz et al. 1993b) may signal cold and explain the abnormalities of cold sensation that occur in patients with injuries of the nervous system (Frühstorfer and Lindblom 1984).

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