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Neural mechanisms of reflex inhibition of heart rate elicited by acupuncture-like stimulation in anesthetized rats

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ABSTRACT

We briefly review our recent studies on the neural mechanisms of the reflex effects of acupuncture-like stimulation on heart rate in rats. In pentobarbital anesthetized rats, acupuncture-like stimulation of one of various segmental areas of the body (forelimb, chest, abdomen, hindlimb) invariably induces a decrease in heart rate. In the case of the hindlimb, the effect can be produced by stimulation of the muscles alone but not of skin alone, and is abolished by severance of the hindlimb somatic nerves. Electrical stimulation of groups III and IV nerve fibers (in the tibial nerve) decreases heart rate. Decrease in heart rate by acupuncture-like stimulation of a hindlimb is accompanied by a decrease in cardiac sympathetic nerve activity, and is abolished by cardiac sympathectomy but not by vagotomy. High spinal cord transection or infusion of the $GABA_A$ receptors antagonist, bicuculline, into the cisterna magna is effective in disrupting the reflex bradycardia. Opioid receptor blockade does not disrupt the reflex arc. We conclude that the reflex pathway involved in the decrease of heart rate by acupuncture-like stimulation comprises groups III and IV muscle afferent nerves whose activation stimulates GABAergic neurons in the brainstem and inhibits sympathetic outflow to the heart. When the sympathetic tone is high due to hypercapnia, the induced reduction in both cardiac sympathetic nerve activity and heart rate is not augmented, suggesting that the magnitude of sympatho-inhibitory response to acupuncture-like stimulation does not depend on pre-existing sympathetic tone.

1. Introduction

Acupuncture has been used to improve visceral autonomic malfunctions (Filshie and White, 1998; O'Connor and Bensky, 1975; Stux and Pomeranz, 1987). Acupuncture studies performed on anesthetized animals have shown that acupuncture-like stimulation elicits reflex responses in various visceral activities, for example, gastric motility (Sato et al., 1993), bladder contraction (Sato et al., 1992), blood pressure (Ohsawa et al., 1995), and adrenal medullary secretion (Sato et al., 1996). The acupuncture-like stimulation-induced responses are reflexes in which the afferent limb are cutaneous and/or muscle somatic afferent nerve fibers, the efferent limb are autonomic efferent nerve fibers, and the reflex centers are in the spinal cord and/or in the brainstem (see reviews by Sato et al., 1994, 1997, 2002).

Acupuncture has been used clinically for the treatment of cardiac dysfunctions, including cardiac arrhythmias such as supraventricular tachycardia (Berman, 1973; Middlekauff, 2004; Sternfeld et al., 1986, 1989; Van Wormer et al., 2008) and acupuncture slows the heart rate in healthy human subjects (Table 1). Concerning the efferent neural pathways of the acupuncture-induced bradycardia in humans, the conclusions are inconsistent between different studies, i.e., it has been suggested that bradycardia is due either to activation of cardiac vagal nerve fibers (Haker et al., 2000; Huang et al., 2005; Lee et al., 2010; Sugiyama et al., 1995), or inhibition of sympathetic nerve fibers (Sakai et al., 2007), or to both (Nishijo et al., 1997; Wang et al., 2002). In human subjects, it is difficult to investigate the neural mechanisms of acupuncture-induced bradycardia, because visceral functions, and notably heart rate, are influenced by emotions triggered by various kinds of stimuli including acupuncture, and also experimental techniques are limited to indirect methods such as administration of autonomic blocker, or analysis of heart rate variability. Clearly, it is advantageous to study the neural mechanisms of acupuncture by direct experimental methods such as the use of denervations or the recording of the electric nerve activity in anesthetized animals, in which all emotional factors are eliminated. Here we present a brief overview of our recent studies on the neural mechanisms of acupuncture-induced bradycardia in rats under general anesthesia (Uchida et al., 2007, 2008, 2010).

2. Heart rate responses to acupuncture-like stimulation of various segmental areas

Adult male Wistar rats were anesthetized initially with pentobarbital (50 mg/kg, i.p.), and maintained under a continuous infusion of pentobarbital in saline (5-8 mg/h, i.v.). The trachea of the anesthetized rat was cannulated, and respiration artificially maintained. The end-tidal CO_2

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Table 1
Manual acupuncture on heart rate in healthy human subject.

Heart rate	Stimulated area/point	HRV		Possible efferent mechanism	Reference
		HF	LF or LF/HF		
↓	lower leg			↑↑ vagal>↑ symp (↑muscle symp. n. activity)	Sugiyama et al. (1995)
↓	forearm			↑ vagal & ↓ symp (blocked by β blocker & muscarinic blocker)	Nishijo et al. (1997)
→	ear	↑	→	↑ vagal	Haker et al. (2000)
↓	hand	↑	↑	↑↑ vagal>↑ symp	
→	hand & lower leg				Middlekauff et al. (2001)
↓	head	↑	↓	↑ vagal & ↓ symp	Wang et al. (2002)
↓	forearm				Imai & Kitakoji (2003)
↓	forearm	↑	→	↑ vagal	Huang et al. (2005)
↓	shoulder	→	↓	↓ symp	Sakai et al. (2007)

↓: decrease, →: no change, ↑: increase, HRV: heart rate variability, HF: high frequency component, LF: low frequency component.

concentration was kept at about 3.0%, and core body temperature at around 37.5 °C. The common carotid artery was cannulated for measurement of systemic arterial pressure. Heart rate was measured with a pulse rate tachometer triggered by systolic blood pressure waves and recorded continuously. Acupuncture-like stimulation was delivered by means of an acupuncture needle (Seirin, Shizuoka) with a diameter of 300-340 μm (No. 8 and No. 10). The needle was inserted, either vertically or obliquely, through the skin to a depth of about 5 mm, then twisted right and left about twice every second for 1 min. Stimulation, affecting both skin and muscles simultaneously, was delivered to 4 different areas of the body: forelimb, chest, abdomen and hindlimb. In some of experiments of a hindlimb stimulation, the skin and underlying muscles of the hindlimb were separated from each other with the nerves kept intact (as much as possible). Following separation, the stimuli were delivered to either the skin or the underlying muscles.

Acupuncture-like stimulations of forelimb, chest, abdomen or hindlimb all produced decrease in heart rate (Fig. 1A, B). The magnitude and time course of the effect was variable in each rat. The heart rate decreased significantly within 20 s of hindlimb stimulation and reached a minimum at around the end of stimulation. The largest effect of stimulation of a hindlimb was a reduction of about 19 beats/min from the basal level of about 413 beats/min. A significant decrease in heart rate continued for about 40 s after the end of hindlimb stimulation. There was no significant difference in the magnitude and time course of heart rate changes when different areas (forelimb, chest, abdomen, hindlimb) were stimulated, as they were equally effective in eliciting the response. During stimulation there was also a fall in blood pressure in parallel to the heart rate changes; this observation rules out the possibility that the bradycardia that was observed might have been a secondary effect of a pressor response (i.e., a baroreflex), as it is a rise and not a fall in blood pressure that would cause bradycardia. Using stimulation of the hindlimb, we further analyzed the neural mechanisms involved in the acupuncture-induced bradycardia.

3. Contribution of the autonomic efferent fibers to the heart as the reflex efferent pathway

The bradycardiac response was not modified after bilateral section of the vagal nerve at cervical level, but was abolished by bilateral section of cardiac sympathetic nerves (stellectomy). With direct recording from cardiac sympathetic nerves we showed that a decrease in cardiac sympathetic nerve activity was the neural basis of the bradycardia elicited by acupuncture-like stimulation of a hindlimb (Fig. 1C, D). The cardiac sympathetic nerve activity changed in parallel to the heart rate changes. Significant decreases in nerve activity were evident within 20 s after the onset of stimulation and activity reached its minimum near the end of stimulation. The average minimal cardiac nerve activity level was about 73% of the prestimulus value. A significant decrease in cardiac sympathetic nerve activity continued for about 40 s after the end of stimulation. These results indicate that heart rate changes are the result of a decrease in sympathetic outflow to the heart rather than an increase in parasympathetic outflow. However, it is not possible to exclude a vagal component in the reflex response, since some anesthetics, including pentobarbital, suppress cardiac vagal efferent activity (O'Leary and Jones, 2003; Sato et al., 1997), and we cannot say how the response would have differed in awake animals.

4. Cutaneous and muscle afferent nerves, and afferent fiber groups (groups I-IV) as the reflex afferent pathway

The bradycardiac response to acupuncture-like stimulation of a hindlimb was completely abolished after severance of sciatic and femoral nerves ipsilateral to the hindlimb stimulated. This result indicates that afferent nerve fibers are necessary for eliciting responses of heart rate following acupuncture-like stimulation. By applying separate stimulation of skin and muscles of the hindlimb, we examined the relative importance of skin and muscles. Acupuncture-like stimulation applied to the skin and muscles of the hindlimb together decreased heart rate (Fig. 2A). However, when skin and muscles were stimulated separately, only the stimulation of the muscles was effective (Fig. 2B, C). The results show that the bradycardiac response depends on the afferent fibers from the muscle rather than on those from the skin.

The importance of muscle afferent nerves for acupuncture-like stimulation was also observed by Ohsawa et al. (1995) in anesthetized rats. The authors demonstrated that acupuncture-like stimulation to the muscles produces a depressor response, but stimulation to the skin does not. In contrast, other studies found that both cutaneous and muscle afferents are important for producing reflex responses of gastric (Sato et al., 1993) and vesical motility (Sato et al., 1992) to acupuncture-like stimulation in anesthetized rats, although muscle afferents played the dominant role.

Concerning the types of afferent nerve fibers involved in acupuncture signals, we have shown that manual acupuncture needle stimulation to the hindlimb activates all four groups (groups I-IV) of afferent nerve fibers in rats (Kagitani et al., 2005). To define the fiber groups involved in the afferent limb of the reflex bradycardia, we used electrical stimulation of the tibial nerve, at the level of popliteal fossa, which innervates hindlimb muscles (Greene, 1963). Repetitive electric stimulation with the maximum intensity to excite groups I and II fibers (0.2 V) with 0.5-50 Hz, produced no obvious response in heart rate (Fig. 3A). Stimulation with 1.0 V, a supra-maximal intensity for group I, II and III fibers, but sub-threshold for group IV fibers, and with 50 Hz, produced a decrease in heart rate (Fig. 3B). Stimulation with 10 V, a supra-maximal intensity for all groups including group IV fibers, with 0.5, 2 and 50 Hz, produced an even larger decrease in heart rate (Fig. 3C). These results suggest that group III and IV fibers in the muscle afferent nerves are responsible for the bradycardiac response by acupuncture. Fibers from both groups III and IV mediate the reflex inhibition of bladder contraction (Sato et al., 1980), and the reflex elevation of cerebral cortical blood flow (Uchida et al., 2000). The reflex inhibition of sympatho-adrenal medullary

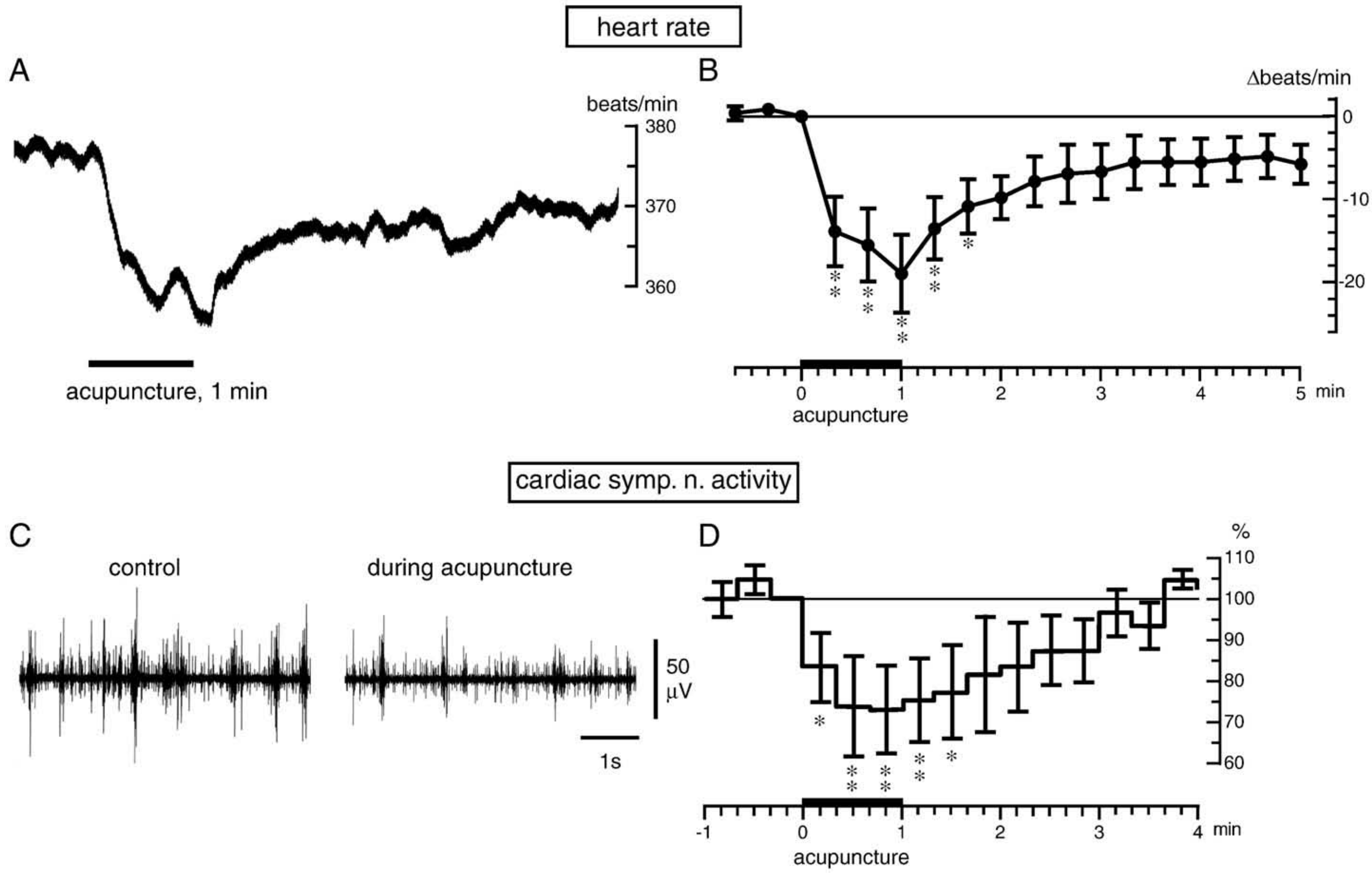

Fig. 1. Effects of acupuncture-like stimulation of a hindlimb on heart rate and cardiac sympathetic nerve activity. A: Sample recording of heart rate. B: Summary of heart rate responses. Changes in heart rate compared with the prestimulus basal values (at 0 min) were plotted every 20 s. Each point and vertical bar depicts the mean ± SEM of the change in heart rate in beats/min for 7 rats. Stimulation was applied for 1 min. C: Sample recordings of cardiac sympathetic nerve activity before (left) and during (right) acupuncture-like stimulation of a hindlimb. D: Summary of the responses of cardiac sympathetic nerve activity. Cardiac sympathetic nerve activity for 5-s period was calculated every 20 s and expressed as a percentage of the prestimulus nerve activity (N = 5 rats). $^{*}p<0.05$, $^{**}p<0.01$; significantly different from prestimulus basal values using one-way repeated measures ANOVA followed by Dunnett's multiple comparison test. Modified from Uchida et al. (2007, 2008).

function, in contrast, is mediated by afferent fibers of groups II and III (Isa et al., 1985).

5. Modulation by sympathetic tone of sympatho-inhibitory response of the heart by acupuncture-like stimulation of a hindlimb

It has been considered that the sympatho-inhibitory response to acupuncture-like stimulation is prominent when the sympathetic tone is high, such as in SHR (spontaneous hypertensive rats) (Thorén and Ricksten, 1979; Sato et al., 1986; Yao et al., 1981, 1982). We experimentally produced increase in basal activity of cardiac sympathetic nerves by hypercapnia as tested by Fukuda et al. (1989), and we examined whether the sympatho-inhibitory response of the heart to acupuncture-like stimulation of a hindlimb is modulated by the sympathetic tone. In the control condition, the end-tidal CO_2 concentration was set at 3.0%. As the end-tidal CO_2 concentration was increased from the control level of 3.0%, to 5.0, 7.0, and 9.0%, the resting activity of the cardiac sympathetic nerve was significantly and progressively increased (Fig. 4A). In contrast, the decrease in cardiac sympathetic nerve activity (Fig. 4B) and heart rate (Fig. 4C) by acupuncture-like stimulation of the hindlimb was significantly less noticeable. Concerning the reason for the discrepancy between our results in this work and the reports of Yao et al. (1981, 1982), we speculate that condition of chronically increased sympathetic tone in SHR, and condition of acutely increased sympathetic tone as a result of hypercapnia, are different and these two different conditions might differently modulate the effects of acupuncture. Makeham et al. (2004) reported that excitatory reflex in the splanchnic sympathetic nerve activity induced by hindlimb stimulation is inhibited when the sympathetic tone is raised by hypercapnia. Our present results show that not only sympatho-excitatory reflex as reported by Makeham et al. (2004) but also sympatho-inhibitory reflex induced by hindlimb stimulation become reduced when the sympathetic tone is raised by hypercapnia. Our study suggests that the efficacy of the sympatho-inhibitory effects of acupuncture upon heart rate become small under the clinical case of hypercapnia. Vickland et al. (2009) reported that physiological response to acupuncture measured by heart rate variability in healthy human subjects is influenced by the state of anxiety in that this may affect the sympathetic tone. Also, the well-known variability in the effect of acupuncture in different individuals may be related to the aetiology of the condition being treated, on gender, on emotional state and other factors (Lundeberg and Lund, 2009).

6. Central components (spinal or supraspinal) and transmitters (opioid or GABA) in the heart rate reflex response following acupuncture-like stimulation

After spinal cord transection at the 1st cervical level, the bradycardiac response to acupuncture-like stimulation of a hindlimb was completely abolished (Fig. 5A). This indicates that the reflex center for the bradycardiac responses by acupuncture-like stimulation is located in the brain. Importance of the brain has also been reported in

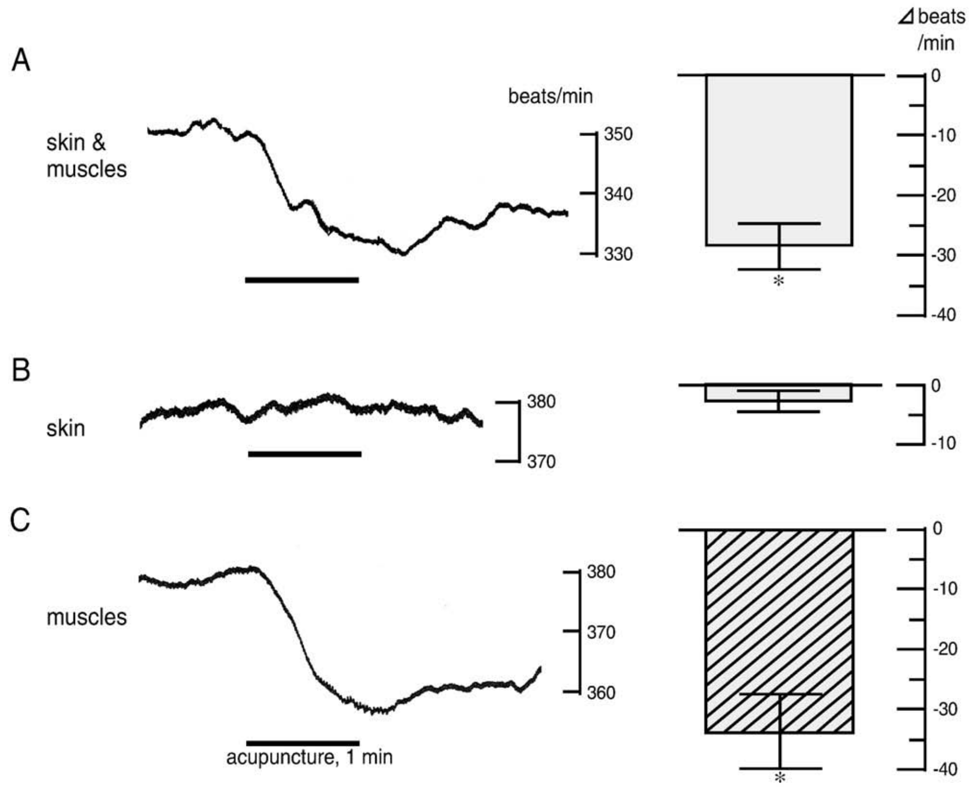

Fig. 2. Responses of heart rate to acupuncture-like stimulation applied to the skin and muscles (A), skin alone (B) or underlying muscles alone (C) in a hindlimb. The changes in heart rate at the end of the acupuncture-like stimulation were compared with the prestimulus basal values. The data are expressed as the mean ± SEM. *p<0.05; significantly different from prestimulus basal values using a paired t-test. N = 8 trials in 4 rats. Modified from Uchida et al. (2007).

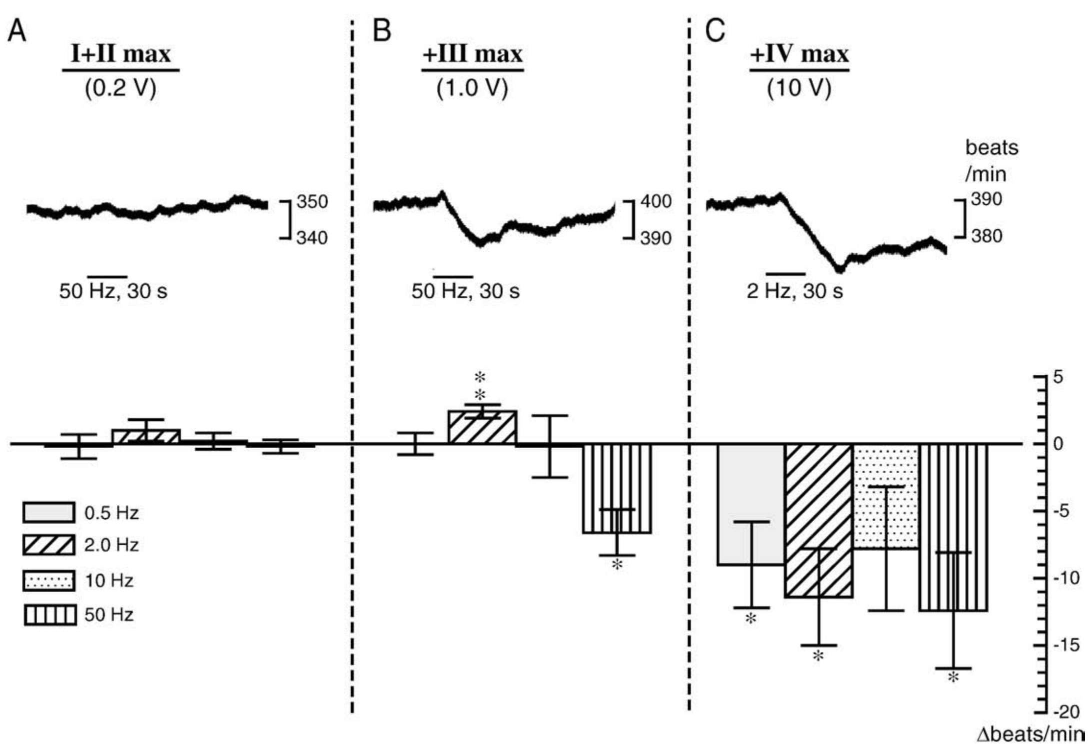

Fig. 3. Changes in heart rate elicited by repetitive electrical stimulation of tibial nerve at various frequencies. Three different stimulus intensities were chosen to activate group I + II fibers only (0.2 V, in A), groups I, II, and III fibers (1.0 V, in B), and groups I-IV fibers (10 V, in C). Trains of stimuli at frequencies of 0.5, 2.0, 10 and 50 Hz were applied for 30 seconds. Upper traces: Sample recordings of heart rate. Lower graphs: Summary of heart rate responses. The changes in mean values of heart rate during 1-min period after the onset of stimulation compared with the prestimulus values for 1-min period from -1 to 0 min were plotted (N = 5 rats). *p<0.05, **p<0.01; significantly different from prestimulus basal values using a paired t-test. Modified from Uchida et al. (2008).

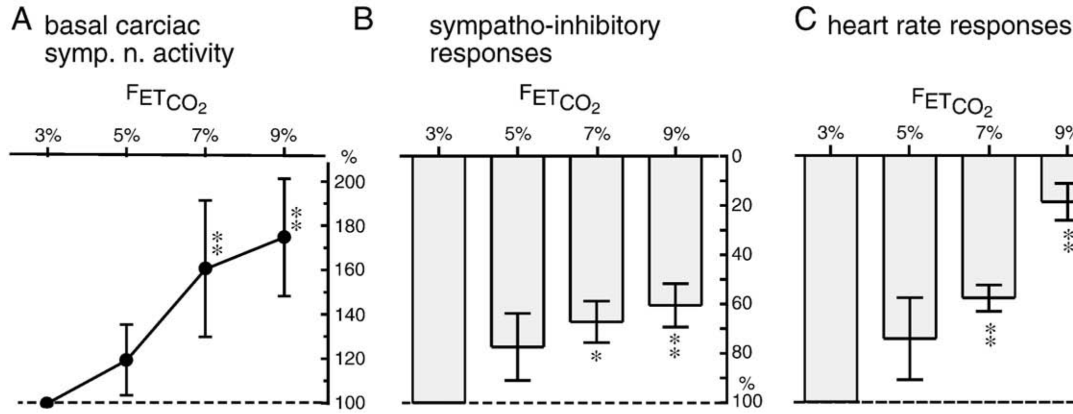

Fig. 4. Changes in cardiac sympathetic nerve activity and heart rate, following acupuncture-like stimulation of a hindlimb under normal control condition and during hypercapia. A: Summary of basal nerve activity during hypercapnia expressed as percentage of corresponding control condition (F_{ETCO2} 3.0%, expressed as 100%). B, C: Summary of responses of cardiac sympathetic nerve activity (B) and heart rate (C). Responses of the cardiac sympathetic nerve or heart rate under control condition (F_{ETCO2} 3.0%) was taken as 100%. Each point or column and vertical bar depicts the mean ± SEM. B: N = 6 rats, C: N = 5 rats. For each rat, 3 trials were averaged. *$p<0.05$, **$p<0.01$; significantly different from the magnitudes of the responses under control condition (F_{ETCO2} 3.0%) using one-way repeated measures ANOVA followed by Dunnett's multiple comparison test. Modified from Uchida et al. (2010).

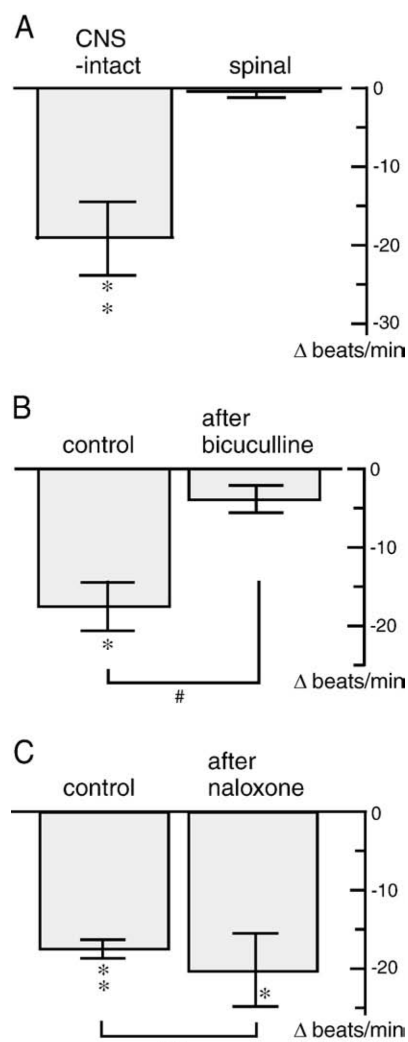

Fig. 5. Attempts to disrupt reflex changes in heart rate by spinal transection (A) or administration of bicuculline (i.c.m., B) or naloxone (i.v., C). The changes in heart rate at the end of the acupuncture-like stimulation of a hindlimb were compared with the prestimulus basal values. A: N = 7 rats, B, C: N = 4 rats. *$p<0.05$, **$p<0.01$; significantly different from prestimulus basal values using a paired t-test. #$p<0.05$; significant differences between the responses by unpaired t-test. n.s.: non-significant ($p>0.05$) difference between the responses by unpaired t-test. Modified from Uchida et al. (2008).

acupuncture-induced blood pressure changes (Li et al., 2009; Ohsawa et al., 1995).

Injection of bicuculline (20 nmol/10 µl) into the cisterna magna (i.c.m.), to block the $GABA_A$ receptor in the brainstem, almost abolished the bradycardiac response elicited by hindlimb stimulation (Fig. 5B). These results suggest that $GABA_A$ receptors in the brainstem have an important role in the bradycardiac responses to acupuncture-like stimulation. Masuda et al. (1992) showed that injection of bicuculline into the rostral ventrolateral medulla (RVLM) diminishes the inhibitory component of somato-sympathetic reflex in anesthetized rabbits. Therefore, we speculate that $GABA_A$ receptors in the RVLM mediate the reflex bradycardia elicited by acupuncture-like stimulation.

Electroacupuncture produces an increase in level of endorphins in the cerebrospinal fluid in rats (Pert et al., 1981). Some acupuncture analgesia has been shown to be naloxone reversible (Bing et al., 1990; Han, 2004; Mayer et al., 1977; Pomeranz and Chiu, 1976). It can be argued that an activation of central opioid systems induced by acupuncture-like stimulation may contribute to the responses observed in our study. However, the bradycardiac response elicited by acupuncture-like stimulation of a hindlimb was not affected by intravenous administration of naloxone, an opioid receptor antagonist (4 mg/kg, Fig. 5C). This finding indicates that an opioid receptor-mediated transmission is not responsible for the present bradycardiac response induced by acupuncture-like stimulation.

7. Conclusion and remarks

After emotional factors are eliminated by means of anesthesia, acupuncture-like stimulation, applied in rats, to various segmental areas of the body decreases heart rate. The decrease in heart rate elicited by acupuncture-like stimulation of a hindlimb was proven to be a reflex response. Its afferent pathway consists of group III and IV hindlimb muscle afferent nerve fibers; the impulses that are generated activate GABAergic neurons in the brainstem and inhibit the sympathetic outflow to the heart, resulting in bradycardia (Fig. 6).

Heart rate is the parameter most commonly monitored in cardiovascular patients and tachycardia is often associated with cardiac morbidity (Palatini and Julius, 2004; Perret-Guillaume et al., 2009). Our present findings in healthy but anesthetized rats may support the application of acupuncture to patients suffering from certain cardiac dysfunction, for example, tachycardia, because it is able to reduce cardiac sympathetic efferent activity and consequently to lower the heart rate.

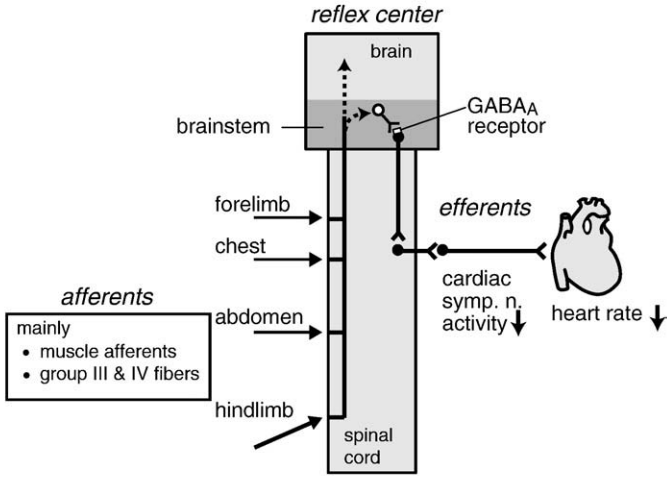

Fig. 6. Schematic drawing of the reflex pathway for heart rate decreases in response to acupuncture-like stimulation. Modified from Uchida et al. (2008).

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