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## Somatic regulation of autonomic functions in anesthetized animals –Neural mechanisms of physical therapy including acupuncture–

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### Abstract

This paper concerns somato-autonomic reflex responses in various visceral organs following somatic sensory stimulation in animals anesthetized to eliminate emotional factors. Various forms of somatic sensory stimulation can produce different autonomic reflex responses, depending on the visceral organs and which somatic afferents are stimulated. Some responses have a dominant sympathetic efferent involvement, whereas others have predominantly parasympathetic efferent involvement. Some responses have propriospinal and segmental characteristics, while others have supraspinal and systemic characteristics in their reflex nature. These somato-autonomic reflex responses may be functioning during physical therapy including acupuncture.

Key words : segmental organization, somato-autonomic reflex, somato-visceral reflex, spinal reflex, supraspinal reflex

Somatic sensory information from the skin, muscles and joints is transmitted to the central nervous system (CNS) by somatic afferent nerves and induces sensation, emotion and reflex responses of motor and autonomic functions. The elucidation of the neural mechanisms of somatically induced autonomic reflex responses, usually called somato-autonomic reflexes, is essential to develop a truly scientific understanding of the mechanisms underlying most forms of physical therapy, including spinal manipulation and traditional as well as more modern forms of acupuncture and moxibustion. We review mainly recent studies on somato-autonomic reflex responses in the cardiovascular system, including

cerebral and peripheral nerve blood flow, digestive, urinary, endocrine and immune systems following somatic sensory stimulation in animals anesthetized to eliminate emotional factors.

### Somato-cardiovascular reflexes

In a majority of anesthetized, artificially ventilated cats and rats, a reflex increase in heart rate and blood pressure is elicited by natural mechanical stimuli, such as noxious pinching or innocuous brushing. Innocuous stimulation produces a weak and inconsistent increase in heart rate and blood pressure, while noxious stimulation causes a consistent marked reflex increase in heart rate and blood pressure<sup>1,10,12,21</sup>.

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Major involvement of cardiac sympathetic nerves in these cardiovascular responses to pinching has been proven indirectly by cutting the cardiac autonomic nerves and directly by recording cardiac autonomic nerve activity<sup>12,21</sup>. In anesthetized rats a reflex increase in heart rate following pinching is not affected by bilateral severance of the cardiac vagal nerves, but abolished by bilateral severance of the cardiac sympathetic nerves. The cardiac sympathetic efferent nerve activity is increased by pinching<sup>12,21</sup>.

In anesthetized rats, the effects on heart rate of pinching stimulation of various segmental skin areas were examined with the spinal cord intact or in the acutely spinalized preparation

(Fig. 1)<sup>12</sup>. In the spinal cord-intact rats, pinching of any segmental skin area is effective, although stimulation of a fore- or hindpaw produces the largest responses. In acutely spinalized rats, pinching applied to the thoracic segmental skin produces the larger response in heart rate, while pinching of a hindpaw becomes ineffective. These results indicate that a strong segmental organization of the cardiac reflex response exists in spinal rats, and this segmental organization is suppressed by supraspinal structures when the spinal cord is intact. In the spinal cord intact preparation, somatic afferents from various segments ascend the spinal cord to the brainstem, and then efferents descend the spinal cord to the thoracic segments and stimu-

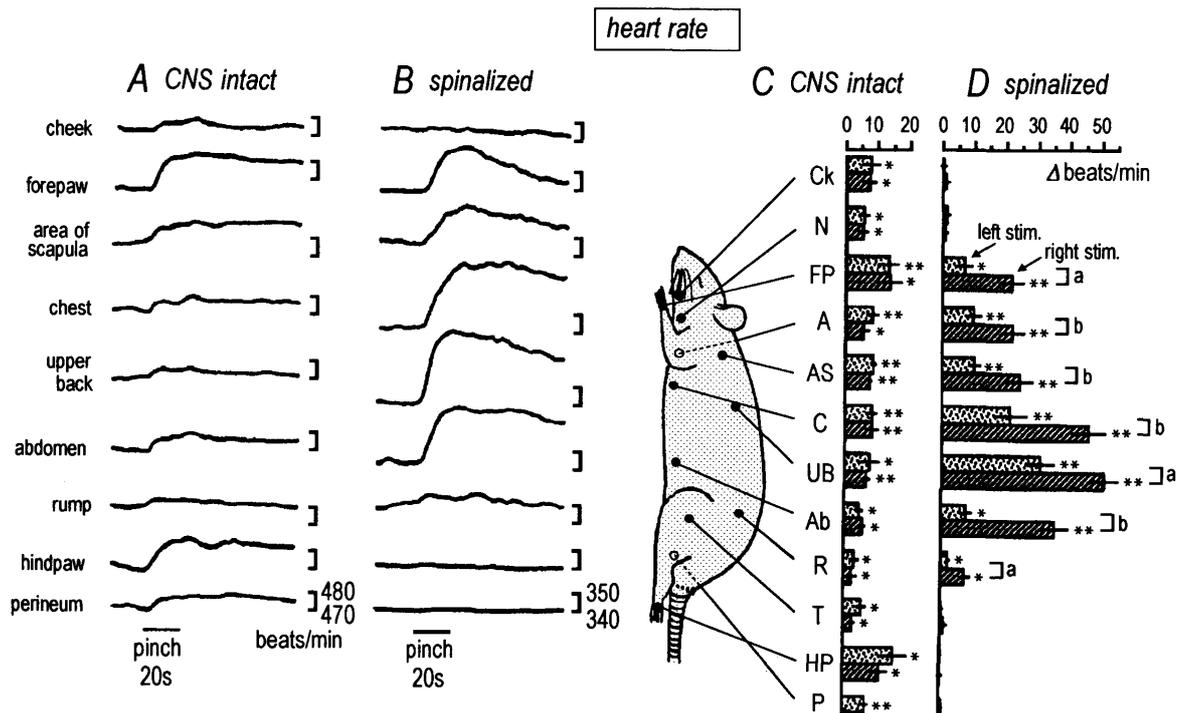


Fig. 1. Effects on heart rate of pinching of various skin areas in anesthetized rats with the CNS intact (A, C) and acutely spinalized at the C2 level (B, D).

A, B: Sample recordings of heart rate responses. C, D: The maximum changes in heart rate in response to left-sided (stippled column) and right-sided (hatched column) stimulation. Ck, cheek; N, neck; FP, forepaw; A, arm (medial side); AS, area of scapula; C, chest; UB, upper back; Ab, abdomen; R, rump; T, thigh (lateral side); HP, hindpaw; P, perineum. In CNS-intact rats, pinching of various segmental areas produced an increase in the heart rate. In spinalized rats, only stimulation of restricted segmental skin areas was effective. \* $P < 0.05$ , \*\* $P < 0.01$ ; significantly different from prestimulus control values, <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$ ; significantly different between responses to left and right side stimulation (From Sato et al.<sup>18</sup>).

late the cardiac sympathetic preganglionic neurons<sup>12)</sup>.

#### Effects of somatic stimulation on cerebral blood flow

It may be an interesting question whether somatic afferent stimulation can produce any reflex response in cerebral blood flow (CBF), because CBF is very important for neuronal activity of the brain.

Pinching of a forepaw in the anesthetized rat can increase CBF in the cortex. After spinal transection at the upper thoracic level, the same stimulation produces the same increase in the cortical CBF without changing systemic blood pressure. The response of cortical CBF exists even after total severance of sympathetic and parasympathetic nerves to the brain. Intracranial cholinergic vasodilative fibers originating in the nucleus basalis of Meynert or substantia innominata and projecting to the cerebral cortex have been hypothesized<sup>17)</sup>. This nucleus is now well known for its profound degeneration during aging or in Alzheimer's disease in human beings. In anesthetized rats focal stimulation, either electrical or chemical, of this nucleus, increases cortical CBF without any changes in blood pressure. This response is reduced by either muscarinic or nicotinic antagonists<sup>4)</sup>. Furthermore, during focal stimulation of this nucleus, acetylcholine (ACh) release in the cortex is increased<sup>15)</sup>. These results indicate that the intracranial cholinergic fibers can dilate small cortical blood vessels and increase cortical CBF.

The neurons in this nucleus are excited by pinching of a paw<sup>2)</sup>. The excitation of these neurons is particularly strong when pinching is applied to a fore- or hindpaw rather than when applied to the face or back. These data of neuronal activity are well in accord with responses of cortical CBF and ACh release<sup>1,16)</sup>. Furthermore, it has been demonstrated that cortical CBF and ACh release in the cerebral

cortex generally increase during walking in conscious rats<sup>13,14)</sup>.

It is concluded that the intracranial cholinergic neurons of the nucleus basalis of Meynert play a vasodilative role in the regulation of blood flow in the cerebral cortex. These fibers can respond to somatic afferent stimulation and produce the observed responses in cortical CBF. The somatic afferent regulation of cortical CBF might be clinically applied to improvement of disturbed or reduced cortical CBF.

#### Effects of somatic stimulation on peripheral nerve blood flow

Peripheral nerves receive their oxygen and nourishment, mainly glucose, from blood flowing in the vasa nervorum. Histochemical studies have demonstrated that the nerve fibers innervating the vasa nervorum contain noradrenaline, acetylcholine, serotonin and various polypeptides.

In our laboratory, it has been demonstrated in rats that nerve blood flow in the sciatic nerve is regulated by (1) sympathetic noradrenergic vasoconstrictors emerging from the ventral roots of the spinal cord via the T11-L1 segments, (2) parasympathetic cholinergic vasodilators emerging from the ventral roots of the spinal cord via the L6 segment, and (3) afferent, calcitonin gene-related peptide (CGRP) containing vasodilators entering the dorsal roots of the spinal cord via the L3-S1 segments<sup>6,26)</sup>.

In spinalized rats, somatic afferent stimulation, for example, pinching of a hindpaw can stimulate sympathetic vasoconstrictor fibers and produce a reflex decrease in nerve blood flow, without changing blood pressure<sup>5)</sup>. After destroying the spinal cord totally below the 10th thoracic level, nerve blood flow is increased by somatic afferent stimulation of the same skin areas<sup>7)</sup>. In this preparation, there is no longer a reflex center. For this response without the spinal cord, we assume that CGRP containing

afferent fibers are branching at least to both the skin and nerve blood vessels. Stimulation of one branch can excite the other branch, releasing CGRP and resulting in vasodilation of the nerve blood vessels. This type of response is presumably a consequence of the axon reflex.

#### Somato-gastrointestinal reflexes

Somato-gastrointestinal reflexes are well known clinically. When patients have stomach pain, they often press the abdominal wall. This procedure is thought to decrease gastric motility. On the other hand, stimulation of the legs has long been considered to facilitate gastric motility.

Pinching of the abdominal skin inhibits gastric motility, while pinching of the paws sometimes facilitates gastric motility in anesthetized rats<sup>9,19</sup>. The inhibitory response persists after spinal transection at the cervical level, but disappears after bilateral severance of the gastric

sympathetic nerves. Gastric sympathetic efferent nerve activity is markedly increased by abdominal pinching. Therefore, the spinal sympathetic reflex is responsible for this gastric inhibition. The facilitatory response disappears, either after spinal transection at the cervical level, or after bilateral severance of the vagal nerves. Gastric vagal efferent nerve activity is increased following hindpaw pinching. Thus, the gastric vagal reflex is responsible for this facilitation<sup>9</sup>.

Recently the effects of acupuncture-like stimulation on gastric motility were examined in anesthetized rats<sup>24</sup>. An acupuncture needle was inserted into the abdominal or hindpaw skin and underlying muscles at a depth of 4–5 mm and was twisted right and left once every second. This stimulation excited both cutaneous and muscle afferent nerve activity and produced gastric responses similar to those to pinching of

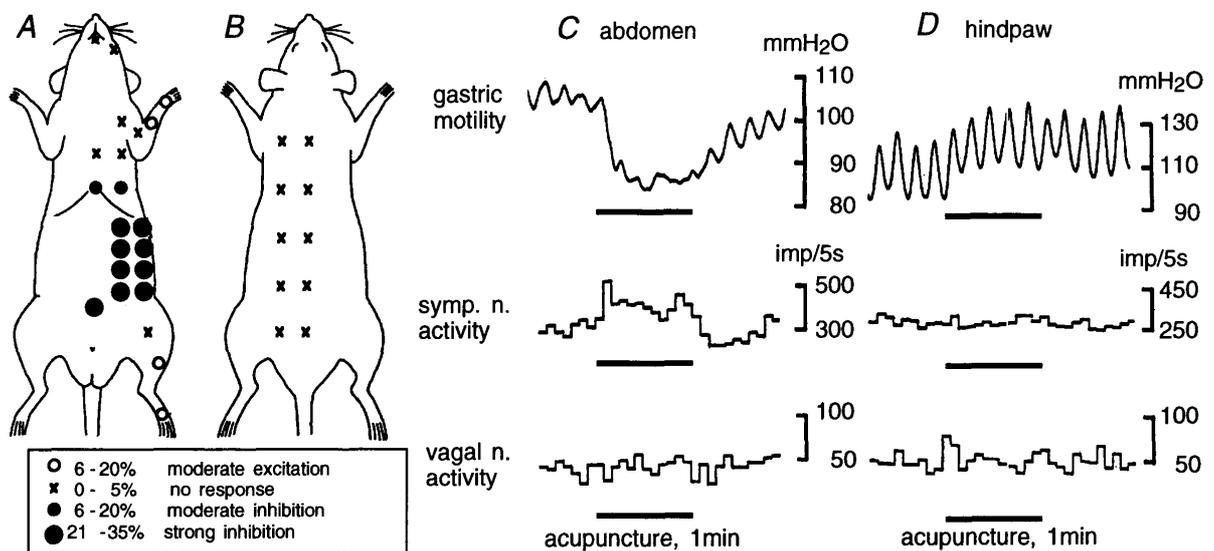


Fig. 2. Effects on gastric function of acupuncture-like stimulation in anesthetized rats.

A, B: Effect on gastric motility of acupuncture-like stimulation of various segmental areas. Open and filled circles indicate the areas where acupuncture-like stimulation caused excitatory and inhibitory gastric responses, respectively. The size of the circle indicates the magnitude of the response, as shown in the bottom inset. C, D: Effects on the gastric motility (upper trace), gastric sympathetic efferent nerve activity (middle trace) and vagal efferent nerve activity (bottom trace) following acupuncture-like stimulation of the abdomen (C) and hindpaw (D). Nerve activity was counted consecutively every 5 s. Stimulation for 1 min is indicated by the bars. The gastric motility, sympathetic and vagal efferent nerve activity were recorded in different rats (From Sato et al.<sup>24</sup>).

skin (Fig. 2). Acupuncture-like stimulation of points on the lower chest or over a wide portion of the abdomen inhibited gastric motility. Stimulation of a forelimb or a hindlimb produced moderate excitation of gastric motility. The acupuncture-like stimulation of other areas, such as the face, upper chest and back had no effect. Gastric sympathetic efferent nerve activity is increased by abdominal stimulation and vagal efferent nerve activity is increased following hindpaw stimulation. The gastric responses to abdominal and hindpaw stimulation disappear after severance of the spinal nerves and hindlimb nerves, respectively. These results indicate that the inhibitory gastric response elicited by abdominal acupuncture-like stimulation is a reflex response. Its afferent nerve pathway is composed of abdominal somatic afferent nerves, the efferent nerve pathway is the gastric sympathetic nerve, and the reflex center is within the spinal cord. The excitatory gastric response elicited by abdominal acupuncture-like stimulation of a hindpaw is also a reflex response. Its afferent nerve pathway is composed of hindpaw somatic afferent nerves, the efferent nerve pathway is the gastric vagal efferent nerve, and its reflex center is within the brain.

#### Somato-vesical reflexes

Clinically, urinary bladder function is known to be controllable by cutaneous stimulation and this is used to facilitate or prevent urination.

The nearly empty or slightly expanded urinary bladder produces only small spontaneous contractions. Brushing or pinching stimulation of the perineal skin provokes a transient increase in intravesical pressure associated with a reflex increase in pelvic parasympathetic efferent nerve activity<sup>20,22</sup>. This response of the bladder exists after spinal transection at the cervical level, but disappears after bilateral severance of pelvic parasympathetic nerves. Stimulation of other skin areas is not effective. Therefore, this

excitatory response is a spinal reflex, and the efferent pathway is in the pelvic parasympathetic nerve.

Further expansion of the urinary bladder produces larger, slower, rhythmic micturition contractions of a frequency of approximately once every minute, which are synchronized with rhythmic burst discharges of the pelvic parasympathetic efferent nerve<sup>20,22</sup>. These micturition contractions usually depend on the presence of the brainstem. Brushing or pinching stimulation of the perineal skin inhibits the rhythmic micturition contractions of the bladder. This is a consequence of reflex inhibition of the rhythmic burst discharges of the pelvic parasympathetic nerve. Similar effects were confirmed when acupuncture needle stimulation was delivered (Fig. 3)<sup>23</sup>.

In conclusion, in anesthetized animals, perineal somatic afferent stimulation elicits two types of reflex responses of bladder contraction, and the efferent pathway of these reflexes is in the pelvic parasympathetic nerves. The types of reflex responses depend on the degree of bladder expansion. When the bladder is quiescent, there is an excitatory spinal reflex response. When the bladder is expanded to a certain degree, the large rhythmic micturition contractions appear as a result of rhythmic burst discharges in the pelvic nerve. Perineal afferent stimulation causes a reflex inhibition of these pelvic nerve burst discharges and results in inhibition of the micturition contractions of the bladder.

#### Somato-adrenal medullary reflexes

Some of the endocrine organs are regulated by autonomic nerves. For example, chromaffin cell functions of the adrenal medulla are regulated by adrenal sympathetic nerves. It has been demonstrated that adrenal sympathetic nerve activity and catecholamine secretion (adrenaline and noradrenaline) are reflexly modulated by

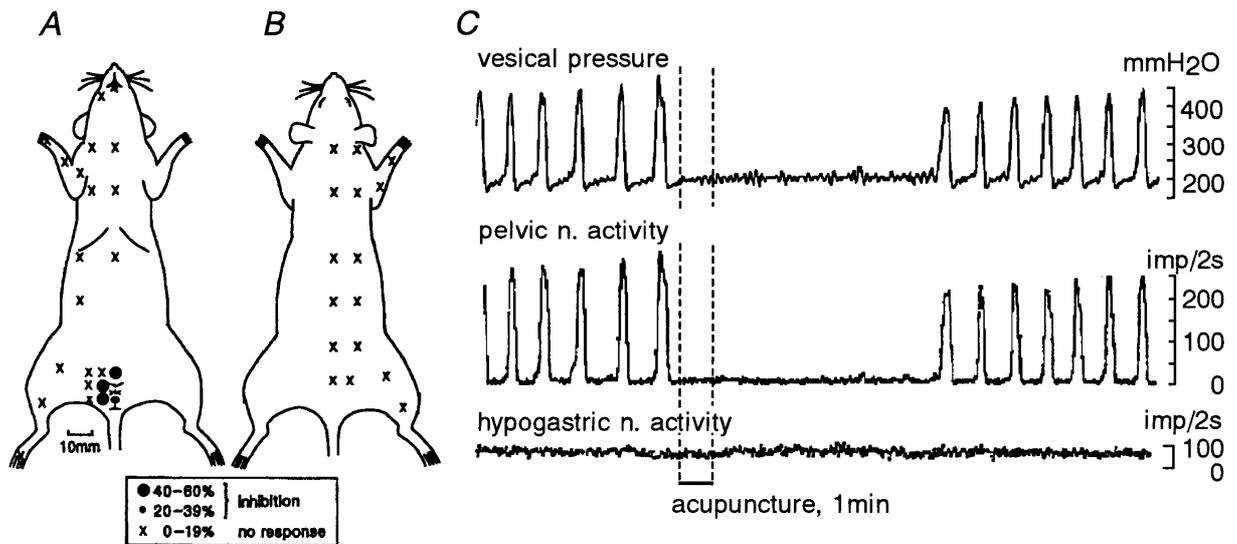


Fig. 3. Effects on vesical function of acupuncture-like stimulation in anesthetized rats.

A, B: Effect on rhythmic micturition contractions (RMC) of acupuncture-like stimulation of various segmental areas. The mean frequency of the RMC for 3 min before the onset of stimulation was taken as 100%, and the changes in mean frequency of the RMC during a 5-min period after the cessation of stimulation was expressed as a percent of this value. The response is indicated according to the bottom inset. C: Effects on the RMC (upper trace), vesical pelvic efferent nerve activity (middle trace) and hypogastric efferent nerve activity (bottom trace) following acupuncture-like stimulation of the perineal area. Nerve activity was counted consecutively every 2 s. Stimulation for 1 min is indicated by the bar and vertical dashedlines (Modified from Sato et al.<sup>23</sup>).

somatic afferent stimulation in anesthetized rats<sup>3,25</sup>). Pinching of the skin produces reflex increases, while brushing of the same skin produces reflex decreases and acupuncture-like stimulation may produce three types of responses (e.g., decrease, increase and no change) in adrenal nerve activity and catecholamine secretion.

In CNS-intact rats the responses of adrenal sympathetic nerve activity following pinching of various segmental areas are systemic. After spinal transection at the cervical level, effective skin areas become restricted to the thoracic segments. Considering the reflex pathways, it appears that a strong segmental excitatory reflex within the spinal cord is mixed with a systemic supraspinal reflex in the CNS-intact animals.

In the case of brushing or acupuncture-like stimulation, effective areas of stimulation are

broad in CNS-intact rats and are restricted to the thoracic segments after spinal transection. Furthermore, the inhibitory reflex response following brushing or acupuncture-like stimulation seen before spinal transection is reversed to an excitatory one after spinal transection. The results of brushing or acupuncture-like stimulation can be summarized by saying that the spinal reflex is excitatory in the spinal animal, and this excitatory spinal reflex is modulated to a systemic inhibitory reflex in the CNS-intact animal.

#### Somato-immune reflexes

Another interesting question might be whether somatic afferent stimulation can affect immune function through sympathetic or parasympathetic efferent nerves that innervate the immune-related lymphatic organs, such as the thymus, spleen, lymph nodes, and bone marrow.

The spleen, for example, receives sympathetic innervation. Stimulation of a splenic sympathetic nerve can constrict splenic blood vessels and reduce blood flow, and also decrease activity of the immune-associated splenic natural killer cells<sup>11</sup>).

Our study in anesthetized rats demonstrated that pinching the hindpaws increased splenic sympathetic efferent nerve activity<sup>11</sup>) and decreased splenic blood flow. We also investigated the effects of brushing and pinching stimulation of the skin on the cytotoxic activity of the natural killer (NK) cells. Brushing of the body surface for 30 min did not significantly influence the cytotoxic activity of the NK cells. However, cytotoxic activity of the NK cells was significantly reduced following pinching of the hindpaws for 30 min. Pinching for 20 min was ineffective. The response of the NK cells was abolished, either after bilateral severance of the splenic sympathetic nerves or after spinal cord transection at the cervical level<sup>11</sup>).

On the other hand, in spinalized rats, pinching stimulation of the abdominal skin for 30 min reduced cytotoxic activity of splenic NK cells by reflexly increasing splenic sympathetic nerve activity<sup>8</sup>). These results indicate that spinal and supraspinal pathways are involved in these reflex responses depending on the cutaneous segments stimulated, e.g., the spinal reflex pathway acts when the abdomen is stimulated, and the supraspinal reflex pathway is involved when the hindlimbs are stimulated.

#### Summary and conclusion

All evidence introduced herein indicates that, in anesthetized animals in which emotional factors have been eliminated, somatic afferent nerve stimulation can reflexly regulate various visceral functions. The contribution of the sympathetic and parasympathetic efferent nerves to the somato-visceral reflexes depends on the organs. Physical therapy, including acupunc-

ture, can be understood as one of various forms of somatic afferent stimulation that produce reflex visceral responses.

One conclusion emerging from the evidence presented is that the effects of somatic afferent stimulation are dependent upon the particular organs and on the spinal afferent segments. When the CNS is intact, the responses can often be broadly elicited as with CBF, heart rate, adrenal medullary hormonal secretion and splenic immune function. However, sometimes the responses have a strong segmental organization, as seen in gastric motility and urinary vesical contractility. Needless to say, in the spinalized preparation all responses are strongly segmental.

Somatic afferent fibers from the limbs enter the spinal cord at the cervical and lumbar enlargements. These regions contain large tracts of somatic motor neurons, and so readily mediate somato-somatic reflexes in the limbs. These same regions, however, are essentially devoid of autonomic preganglionic neurons. Hence, stimulation of limb afferents may induce visceral responses, through supraspinal centers (Fig. 4)<sup>18</sup>). Since such centers would be called upon to integrate input from throughout the body, the elicited responses would tend to be systemic rather than segmentally organized or target organ-specific. On the other hand, the thoracic-upper lumbar cord and the 2nd-4th sacral segments contain sympathetic and parasympathetic preganglionic neurons, respectively. Somatic afferent fibers entering the spinal cord at these levels may synapse with local autonomic neurons as well as with projections to supraspinal somato-autonomic reflex centers (Fig. 4)<sup>18</sup>). Such input could well elicit localized or target organ-specific responses.

The somatically-induced reflex responses of autonomic, hormonal and immune functions demonstrated in anesthetized animals, as have been discussed herein, appear to function even during conscious states. We need further studies to

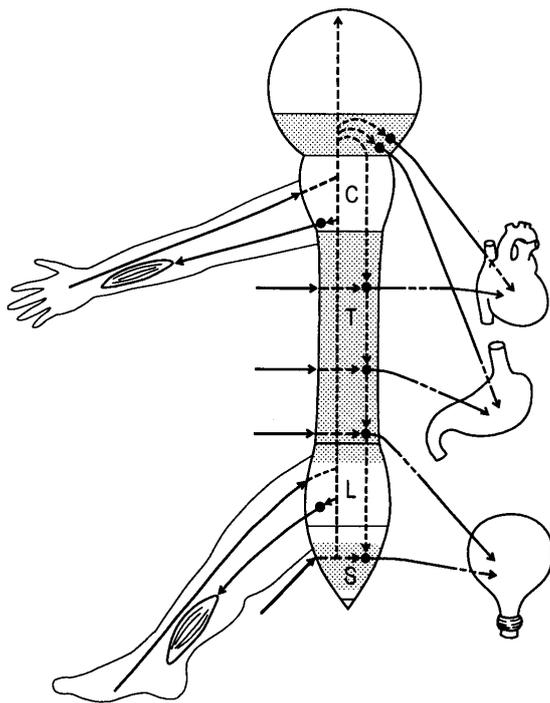


Fig. 4. Reflex pathways for the somato-somatic and somato-autonomic reflexes.

Somatic motor neurons innervating limbs are contained in the spinal cord at the cervical and lumbar enlargements. Limb afferents readily synapse with somatic motor efferents to elicit potent spinal reflexes. These spinal segments, however, are essentially devoid of autonomic preganglionic neurons. Thus somato-autonomic reflexes elicited by stimulation of limb afferents appear to be mediated mainly at the supraspinal level. On the other hand, stimulation of segmental afferents may elicit responses from both supraspinal and spinal reflex centers. Spinally mediated somato-autonomic reflexes may show a very strong segmental organization and, under the appropriate conditions, the effects on target organs may be quite specific. Often, however, in the CNS-intact animal, these spinal reflexes are masked by descending influences from the brain. Broken lines in this figure indicate synaptic pathways, not direct axonal pathways. Shaded areas of the CNS indicate regions which contain the autonomic preganglionic neurons (From Sato et al.<sup>18</sup>).

evaluate the physiological meaning of these somato-autonomic reflex responses. The analysis of neural mechanisms of these reflex responses seems to be very important for clinical application

to regulate visceral function by physical treatment.

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