

CRPS is a Disease of the CNS. **The Disturbed Communication between brain and Body** *Wilfrid Jänig*

Introduction

For almost a century it is discussed that activity in the sympathetic nervous system may be involved in the generation of pain, e.g., in causalgia and reflex sympathetic dystrophy. This assumption is based mainly upon two observations: (1) the pain is spatially correlated with signs of autonomic dysfunction, i.e., with abnormalities in blood flow and sweating, as well as with trophic changes, and (2) blocking the efferent sympathetic supply to the affected part relieves the pain. In 1995 the terminology of these pain syndromes was changed and is now based entirely on elements of history, symptoms and findings on clinical examination with no implied pathophysiological mechanism. Reflex sympathetic dystrophy and causalgia are now called Complex Regional Pain Syndromes (CRPS). In CRPS type I (reflex sympathetic dystrophy) minor injuries at the limb or lesions in remote body areas precede the onset of symptoms. CRPS type II (causalgia) develops after injury of a major peripheral nerve [16,21]. CRPS patients presenting with exactly the same clinical signs and symptoms can be divided into two groups by the negative or positive effect of sympathetic blockade. The pain component that is relieved by specific sympatholytic procedures is considered "sympathetically maintained pain" (SMP). Thus, *SMP* is defined to be a *symptom* and *not a clinical entity*. I will first present a hypothesis stating that CRPS is a disease of the central nervous system and argue on which clinical and experimental data this hypothesis is based with special focus on the sympathetic nervous system.

CRPS is a neuronal disease involving the central nervous system (Fig. 3, 19)

The hypothesis is put forward that the sensory, sympathetic, somatomotor, and trophic changes (including swelling), observed in variable combinations in patients with CRPS are the results of changes and distorted processing of information in the central nervous system. Various levels of integration probably are involved such as spinal cord, brain stem, diencephalon (hypothalamus, thalamus), and telencephalon (cortex and limbic system). A key player in generation and maintenance of CRPS is most likely the nociceptive system. However, this system must not be seen to *cause* CRPS in the sense that CRPS can be reduced to the malfunctioning of the nociceptive system. Furthermore, although the sympathetic nervous system is important, CRPS cannot be reduced to a malfunctioning of this system or components of it. Arguments supporting that CRPS is a central nervous system disease will be discussed. Table 1 lists clinical and experimental observations made on patients with CRPS that clearly support this contention.

Table 1 Arguments for central and for peripheral changes in CRPS I

CENTRAL CHANGES

1. Changes of regulation by sympathetic systems (1 in Fig. 3)

- ∩ Thermoregulatory reflexes in cutaneous vasoconstrictor neurones reduced
- ∩ Respiration elicited reflexes (generated by deep in- and expiration) in cutaneous vasoconstrictor neurones reduced
- ∩ Changes of activity in sudomotor neurones (sweating)
- ∩ Swelling reduced by sympathetic blocks

2. Sensory changes (2 in Fig. 3)

- ∩ Mechanical allodynia (quadrant, hemisensory)
- ∩ Hypoesthesias (mechanical, cold, warm; hemisensory, quadrant)
- ∩ Bilateral distribution of hypo- and hyperesthesias (mechanical, cold, warm, heat)

3. Somatomotor changes (3 in Fig. 3)

- ∩ Active motor force and active range of motion reduced
- ∩ Physiological tremor increased
- ∩ Poor motor control and coordination of movement; altered gait and posture
- ∩ Dystonia
- ∩ Sensory-motor body perception disturbance

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4. Initiating events (4 in Fig. 3)

- ∩ Out of proportion to pain disease (minor trauma)
- ∩ Events remote from affected extremity (e.g., in the visceral domain)
- ∩ Central (e.g., after stroke; related to endogenous control systems?)

5. Pain relief by sympathetic blocks with local anaesthetics (5 in Fig. 3)

- ∩ Relief of pain *outlasts conduction block* by an order of magnitude, (i.e., a temporary block is followed by a *long-lasting* pain relief)
- ∩ A few temporary blocks are sometimes sufficient to generate permanent pain relief
- ∩ *Sympathetic activity maintains a positive feedback circuit* (?)

PERIPHERAL CHANGES

6. Sympathetic-afferent coupling (6 in Fig. 3)

- ∩ After nerve lesion via noradrenaline and adrenoceptors (CRPS II)
- ∩ Indirectly via vascular bed and other mechanisms (CRPS I; deep somatic?)
- ∩ [Indirectly via inflammatory mediators and neurotrophic factors]
- ∩ [Mediated by the adrenal medulla (adrenaline)]

7. Inflammatory changes and oedema (7 in Fig. 3)

- ∩ Neurogenic inflammation (precapillary vasodilation, venular plasma extravasation), involvement of peptidergic afferents (?)
- ∩ Sympathetic fibres mediating effects of inflammatory mediators (e.g., bradykinin) to venules leading to plasma extravasation (?)
- ∩ Involvement of inflammatory cells and immune system (?)
- ∩ Change of capillary filtration pressure (?)

8. Trophic changes (8 in Fig. 3)

- ∩ Long-range consequences of inflammatory changes and oedema (?)
 - ∩ Direct (trophic?) effect of sympathetic and afferent fibres on tissue (?)
- Endothelial damage (?)

Modified from [10]

The scheme of Fig. 3 outlines a general heuristic explanatory hypothesis which has been developed in the last 25 years [13]. This hypothesis puts the clinical findings observed in CRPS patients in relation to the changes in the somatosensory, autonomic and somatomotor systems and postulates that changes in the central representations of these systems must occur in order to explain the clinical findings. The events initiating the clinical symptoms are mostly associated with a trauma in the somatic domains at the extremities, but sometimes also with trauma in the viscera or in the central nervous system. The changes developing after these triggering events usually outlast the trauma by orders of magnitude.

Fig. 3. General explanatory hypothesis about the neural mechanisms of generation of CRPS I and II following peripheral trauma with and without nerve lesions, chronic stimulation of visceral afferents (e.g. during angina pectoris, myocardial infarction) and of deep somatic afferents and, rarely, central trauma. The clinical observations are put in bold lined boxes. Note the vicious circle (arrows in bold black). An important component of this circle is the excitatory influence of postganglionic sympathetic axons on primary afferent neurones. The numbers indicate the changes occurring potentially in CRPS patients that have been quantitatively measured or postulated on the basis of clinical observations (see Table 1): 1, changes in sympathetic neurones; 2, pain, somatosensory changes; 3, changes in somatomotoneurones; 4, initiating events; 5, consequences of sympathetic blocks or sympathectomy (dotted line); 6, sympathetic-afferent coupling (positive vicious feedback circuit [in bold]); 7, “antidromically” conducted activity in peptidergic afferent C-fibres (double dotted arrow) leading to increase of blood flow (arteriolar vasodilation) and venular plasma extravasation, both hypothetically contributing to increase in blood flow, swelling/inflammation and trophic changes. 8, sympathetic postganglionic fibres hypothetically contributing to swelling/inflammation and trophic changes. For details see text. Modified from [13].

1. Sympathetic systems supplying skin (Figs. 4, 5)

Cutaneous vasoconstrictor neurones and blood flow through skin

Thermoregulatory reflexes to whole body heating and cooling are changed in the distal parts of the affected extremity of CRPS patients. During whole body cooling activity in the vasoconstrictor neurones supplying skin is increased leading to decrease of blood flow through the hand and decrease of skin

temperature [7]. Patients with CRPS exhibit pathophysiological patterns of behaviour of the cutaneous vasoconstrictor neurones supplying the affected extremity during thermoregulatory load (whole body cooling and warming) [24]. In the early stages of CRPS type I, cutaneous vasoconstriction and vasodilation in fingers elicited by deep inspiration (and expiration) is reduced or abolished (Fig. 5) [23]. This lack of respiratory modulation of vascular perfusion is not due to damage of the cutaneous vasoconstrictor neurones since the modulation returned after successful treatment of the CRPS in the patient (Fig. 5).

Fig. 5. Changes of cutaneous blood flow through the index finger tips of the affected (right) arm (upper trace) and the contralateral (control) arm (second trace) during deep inspiration (5/min, lower trace) in a patient (a) two weeks after onset of CRPS I before treatment and (b) five weeks after successful treatment and clinical improvement. CRPS I developed after right radius fracture. The treatment consisted of repeated sympatholytic procedures using regional guanethidine blocks combined with the application of a nonsteroidal anti-inflammatory drug and later with physiotherapy. The regional sympathetic blocks significantly reduced the pain showing that the patient had SMP. Five weeks after start of treatment the typical symptoms of CRPS I were significantly reduced but still present. Blood flow was measured by laser Doppler flowmetry. Inspiration was measured by electronic spirometry. Deep inspiration causes phasic activation of cutaneous vasoconstrictor neurones and decrease of cutaneous blood flow. There was a complete loss of function of the cutaneous vasoconstrictor neurones early after onset of CRPS I (no inspiration-induced vasoconstriction) and a complete functional recovery after successful treatment. The loss of function of the cutaneous vasoconstrictor system was central and not due to lesion of the peripheral vasoconstrictor pathway. Modified from [23].

Sudomotor neurones and sweating

Clinical observations described in the literature show that sweating is changed in the affected extremity (hypo- or hyperhidrosis) in CRPS type I patients. Activation of sweat glands always occurs only by its cholinergic innervation and not by circulating substances or local mechanisms. These changes can only be attributed to central changes which then lead to changes of activity in sudomotor neurones [7].

2. Sensory systems of the skin (Figs. 6, 7)

Up to 50% of patients with chronic CRPS I develop hypoesthesia and hypoalgesia on the whole half of the body or in the upper quadrant ipsilateral to the affected extremity showing that these patients have increased thresholds to mechanical, cold, warm and heat stimuli compared with the responses generated from the corresponding contralateral healthy body side. Patients with these extended sensory deficits have longer illness duration, greater pain intensity, a higher frequency of mechanical allodynia, and a higher tendency to develop changes in the somatomotor system than do patients with spatially restricted sensory deficits [18,19]. These findings have considerable implications:

- n The anatomical distribution of the changed painful and non-painful somatosensory perceptions observed in CRPS patients are likely due to changes in the central representation of somatosensory sensations in the thalamus and cortex. This is supported by magnetic encephalographic (MEG) and functional magnetic resonance imaging (MRI) studies of the primary somatosensory cortex, the frontal cortex and parietal cortex [2,15].
- n Generalized sensory deficits are particularly found in patients with chronic CRPS I. These changes may become permanent and irreversible and probably related to plastic cortical changes.
- n The generalized sensory changes are correlated with neglect-like phenomena in these CRPS patients. The common denominator of generalized sensory changes, neglect-syndrome and disuse syndrome may be the changed or absent input in afferent neurones from deep somatic tissues (skeletal muscles, joints, fascia) to the central body representations leading to a mismatch between somatosensory input and central somatosensory and motor body representations. This would then be reflected in a body perception disturbance [6,14].
- n CRPS I patients mostly locate their spontaneous pain into deep somatic structures of the affected extremity. They have furthermore deep somatic mechanical hyperalgesia/allodynia. This raises the question whether the non-painful sensations elicited from muscle and joints are changed too.

Fig. 7. Detection thresholds to cold, warm and heat stimuli (upper rows) and to von Frey filament stimulation (lower rows in *italic*) in CRPS I patients with sensory impairment spatially restricted to the affected side (A) and in CRPS I patients with generalised sensory impairment (B). The thermal stimuli were applied utilising the Peltier effect. Cooling and warm stimuli were applied at a rate of $0.7^{\circ}\text{C}\cdot\text{s}^{-1}$ on a skin surface of 5.8 cm^2 , starting from a reference temperature of $32 \pm 0.5^{\circ}\text{C}$. Heat stimuli were ap-

plied at the same rate and surface, but starting from a reference temperature of 40°C. Detection threshold to von Frey filament stimulation in $\text{g}\cdot\text{mm}^{-2}$. Cooling and warm stimuli applied to face, chest, upper arm, hand and foot (N=14 patients). Heat stimuli applied to chest, upper arm, hand and foot (N=14 patients). Mechanical stimuli with von Frey filaments applied to face, chest, upper arm/thigh and hand/foot (N=24 to 25 patients with limited sensory impairment; N=15 patients with generalised sensory impairment). Generalised sensory changes occur preferentially in chronic CRPS I patients and are correlated with a higher incidence of mechanical allodynia and motor deficits than in CRPS I with spatially restricted sensory changes. Numbers show mean values. Significant differences between left and right are indicated in red (two-tailed paired *t*-test, $p < 0.05$). Modified from [19].

3. Somatomotor changes (Fig. 8)

About 50% of patients with CRPS I show a decrease of active range of motion, increased amplitude of physiological tremor, and reduced active motor force in the affected extremity [5,6]. Other observations include associated movement disorders (myoclonus, dystonia) (see [6]). It is unlikely that these motor changes are related to a peripheral process (e.g., influence of the sympathetic nervous system on neuromuscular transmission and/or contractility of skeletal muscle [see Chapter 12]). These somatomotor changes are more likely generated by changes of activity in the motoneurons, ie, they have a central origin and are possibly related to plastic changes in the somatosensory, motor and premotor cortices [15].

4. Initiating events (Fig. 9)

The clinical signs and symptoms in CRPS are disproportionate to the traumatic events initiating or triggering this syndrome. The local changes generated by the trauma often disappear, yet the syndrome persists. Furthermore, CRPS I in an extremity may be triggered by remote events (e.g., in the viscera) or by events in the central nervous system (e.g., central lesions) In fact it has been proposed that processes in the prefrontal, frontal and parietal cortices that are related to psycho-social changes enhance the clinical signs and symptoms in CRPS or even may initiate them. These clinical observations argue that mechanisms operating in CRPS I cannot simply be explained to be caused by events in the periphery of the body related to the trauma (e.g., sympathetic-afferent coupling or persistent activation of nociceptive afferents).

5. Pain relief by sympathetic blocks (Figs. 10, 11,12)

The sympathetic nervous system may be involved in the *generation* of pain under certain pathophysiological conditions yet not under physiological conditions. Pain dependent on activity in the sympathetic neurones called *sympathetically maintained pain* (SMP [21]) usually includes both spontaneous and evoked pain (i.e. allodynia evoked by mechanical or cold stimuli). It is present in about 60% of patients with acute CRPS (Fig. 12). The concept that the (efferent) sympathetic nervous system is involved in the generation of pain is based on long standing clinical observations. Two groups of experimental studies on patients with CRPS are representative for this extensive work showing in CRPS patients with SMP that noradrenaline injected into painful area mimics SMP [1,22] or that physiological activation of the sympathetic innervation enhances SMP [20]

In CRPS patients with SMP blockade of sympathetic activity to the affected extremity by a local anaesthetic applied to the appropriate sympathetic paravertebral ganglia generates pain relief in the affected extremity for significantly longer time periods compared to saline injected close to the same site (Fig. 11). Thus the pain relieve generated by blockade of sympathetic activity exceeds that produced by a similar placebo "block". The duration of pain relief greatly outlasts the duration of conduction block generated by the local anaesthetic arguing that the pain-relieving effect of sympathetic blocks observed in CRPS patients with SMP cannot be explained simply by temporary blockade of activity in the sympathetic neurones. The long-lasting pain-relieving effects of sympathetic blocks clearly argue that activity in sympathetic neurones, which is of *central origin*, maintains a positive feedback circuit via the primary afferent neurones. We hypothesize that activity in sympathetic neurones maintains a central state of hyperexcitability (e.g., of neurones in the spinal dorsal horn), via excitation of afferent neurones (Fig. 13), which may be initiated by an intense noxious event or by other central events. This central state of hyperexcitability is switched off during a temporary block of conduction in the sympathetic chain lasting only for a few hours and cannot be switched on again when the block wears off and the sympathetic activity, and therefore also the sympathetically-induced activity in afferent neurones, comes back again.

Fig. 11. Sympathetic blocks with a local anaesthetic in CRPS I patients with SMP leads to a long-lasting significant reduction of pain. The local anaesthetic or saline (control) were injected close to the corresponding paravertebral sympathetic ganglia (stellate ganglion in 4 patients, lumbar sympathetic ganglia in 3 patients) in the same group of 7 CRPS I patients. Double-blind crossover study. Pain was measured repeatedly using the visual analogue scale (VAS) on the day of the injection and on 7 days after the injection. Both interventions produced pain relief (see 50% value of pain relief). However, the duration of the mean relief of pain to injection of the local anaesthetic lasted for 6 days and was significantly longer than the mean pain relief following local injection of saline which lasted for 6 hours (placebo block). The initial maximal peaks of relative analgesia were statistically not different. Means + SEM. Modified from [17].

These experiments on human patients clearly argue that, in some CRPS patients, (1) activity in sympathetic neurones is involved in generating pain, (2) blockade of the sympathetic activity relieves the pain, and (3) noradrenaline injected intracutaneously rekindles the pain. Furthermore, it has been shown that most SMP is in the deep somatic tissues and that SMP decreases with respect to time after the initiating event (Fig. 12).

Fig. 12. The component of pain that depends on activity in cutaneous sympathetic noradrenergic neurones (skin SMP) or on activity in sympathetic noradrenergic neurones innervating deep somatic tissues (deep SMP) or is independent of activity in sympathetic neurones (SIP, sympathetically independent pain) over the course of CRPS (modified from [20]).

6. Sympathetic-afferent coupling (Figs. 13-15)

Fig. 14 Concept of generation of peripheral and central hyperexcitability during inflammatory pain and neuropathic pain and the role of the sympathetic nervous system. The upper interrupted arrow indicates that the central changes are generated (and possibly maintained) (a) by persistent activation of nociceptors with C-fibres called here “central sensitisation” or (b) after trauma with nerve lesion by ectopic activity and other changes in lesioned afferent neurones called here “central hyperexcitability”. The lower interrupted arrow indicates the efferent feedback via the sympathetic nervous system or the sympatho-adrenal system to the primary afferent neurones. Primary afferent nociceptive neurones (in particular those with C-fibres) are sensitised or generate ectopic activity. These peripheral changes entail changes of the central representations (of the somato-sensory system) which may become irreversible (and therefore also the central hyperexcitability). The central changes, induced by persistent activity in sensitized afferent nociceptive neurones or after nerve lesions, are also reflected in the efferent feedback systems. The transmission of nociceptive impulses is under multiple control of the brain.

Fig. 15. Relation between afferent neurones and sympathetic neurones following peripheral nerve lesion. Collateral sprouting of unlesioned sympathetic neurones in the dorsal root ganglion (DRG) and in the peripheral target tissue. Up-regulation or uncovering of functional adrenoceptors (preferentially α -adrenoceptors) by afferent neurones after nerve lesion. It is unclear in which way these processes are related to the biochemical signals (e.g. neurotrophins) synthesised by neurones, Schwann cells, and other cells in the DRG or in the periphery and the expression of their receptors. In which way are these processes dependent on activity in the afferent neurones, on the presence/absence of postganglionic noradrenergic neurones or on the activity in the postganglionic neurones? NAd, noradrenaline (from [8,12]).

7. Inflammatory changes and edema (Figs. 16, 17)

The idea that CRPS I patients undergo *inflammatory processes* in the affected extremity, in particular in the deep somatic tissues including bones, goes back to Sudeck who believed that this syndrome is an inflammatory bone atrophy (“entzündliche Knochenatrophie”). Accordingly, bone scintigraphy demonstrates periarticular tracer up-take in acute CRPS and synovia biopsies and scintigraphic investigations with radiolabeled immunoglobulins show protein extravasation, hypervascularity and neutrophil infiltration. Furthermore, in the fluid of artificially produced skin blisters significantly higher cytokine levels (IL-6, TNF-alpha) as well as tryptase (a measure of mast cell activity) were observed in the involved extremity as compared with the uninvolved extremity (see [10]). This is supported by animal studies showing that the sympathetic nervous system can influence the intensity of an inflammatory process and clinical studies showing that sympatholytic procedures can ameliorate pain, inflammation, and oedema in human beings [11,12]. The mechanisms of initiation and maintenance of inflammatory processes occurring in early CRPS and the role of sympathetic postganglionic neurones in it are unclear and remain to be worked out.

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Based on observations following sympathetic blocks, it is a long-standing assumption that swelling (oedema) in the affected limb of CRPS patients is dependent on activity in sympathetic neurones. Spinal anaesthesia may be followed by a decrease of the oedema. This decrease starts within one to two hours and the oedema may disappear within days (Fig. 17). Whether this dependence of the oedema on the sympathetic innervation is related to changes of rate and pattern of activity in sympathetic neurones innervating blood vessels (and/or lymph vessels) or also related to changes in neurovascular transmission is unknown. Furthermore, it cannot be excluded that the oedema is also related to antidromic activity in peptidergic afferent neurones with unmyelinated (C) and small-diameter myelinated (A δ) fibers (see interrupted arrow in Fig. 3). It has been proposed, first, that persistent activation of nociceptors generates strong primary afferent depolarization of the central terminals of these peptidergic afferent neurones in the superficial horn of the spinal cord via GABAergic interneurones, second, that this depolarization generates impulses in these afferent neurones travelling antidromically to the periphery, and, third, that these antidromically conducted impulses produce arteriolar vasodilation in peripheral tissues and are possibly involved in inflammatory processes, i.e. venular plasma extravasation (for review see [25]). However, it must be kept in mind that the swelling is present in many CRPS patients in the entire distal extremity, i.e. far beyond the territory of the site of the trauma. In view of the prominence of the oedema in many CRPS patients (in particular type I) is the lack of knowledge about its underlying mechanism surprising.

An important point is that *temporary* blockade of the sympathetic activity (and/or possibly of the antidromically conducted activity in afferent neurones) appears to interrupt a vicious circle that maintains the oedema (see 6 Fig. 3). The mechanism underlying this vicious circle is unknown (Fig. 17).

Fig. 17. Spinal anaesthesia reduces severe edema in a patient with CRPS I. Female patient, 15 years, 3 months after trauma on foot. No spontaneous pain, cutaneous hyperalgesia or allodynia, but deep hyperalgesia. Implantation of spinal catheter at thoracic level T10 on day 4. Spinal anaesthesia for 43 hours starting on day 7 with 1.4 ml 0.5% bupivacaine/h. Increase of skin temperature of foot to 36°C (indicating complete decrease of activity in cutaneous vasoconstrictor neurones). Significant decrease of oedema in one day and its complete disappearance with time after termination of the spinal anaesthesia together with other symptoms of CRPS I. The decrease of the oedema was considered to be due to decrease of activity in sympathetic neurones. However, it cannot be excluded that antidromically conducted activity in peptidergic primary afferent neurones with unmyelinated axons was blocked. For details see text. Ordinate scale, circumference of lower thigh. Modified from [4].

8. Trophic changes (Fig. 18)

The underlying mechanisms of trophic changes, as prominent as they may be, are entirely unclear. However, based on the observation that these changes may ameliorate after sympathetic blocks, argues that they are related to the sympathetic innervation.

Conclusions (Fig. 19)

Clinical observations, experimentation on humans and experimentation on animals argue that CRPS is primarily a disease of the central nervous system:

1. CRPS patients exhibit alterations of the somatosensory system, the sympathetic nervous system, and the somatomotor system. These alterations are reflected in multiple somatosensory changes (including the perception of tactile, thermal and noxious stimuli), in changes of blood flow and sweating, and in movement disorders indicating that the central representations of these systems are changed (see dots in Fig. 19 and bold-lined boxes in Fig. 3). Thus, CRPS appears to be a disease involving these neuronal systems and their central representations.
2. The peripheral changes (sympathetic-afferent coupling, vascular changes, inflammation, oedema, trophic changes) cannot be seen independently of the central ones. Central nervous system and peripheral body tissues interact with each other via afferent and efferent signals. Although the nature of this interaction is still a puzzle we postulate that it is the mismatch between the afferent and efferent signals, occurring on different levels of integration in the afferent and efferent body maps in the central nervous system, that cause the changed autonomic, sensory and somatomotor reactions.
3. This way of looking at CRPS shifts the attention away from interpreting this syndrome conceptually in a narrow manner and to reduce it to *one* system or to *one* mechanism only, centrally or peripherally. This view will further our understanding why CRPS I may be triggered after a trivial trauma, after a trauma being remote from the affected extremity exhibiting CRPS, after immobilization of an extremity, or following processes in the cerebral hemispheres. It will explain why, in

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CRPS patients with SMP, a few temporary blocks (and sometimes only one block!) of the sympathetic supply to an affected extremity sometimes lead to a long-lasting (even permanent) pain relief and to resolution of the other changes present in CRPS.

4. Using imaging techniques we will learn which central (cortical and subcortical) changes are specific for CRPS and how these central changes are expressed in the efferent (somatomotor and autonomic) systems and the distorted sensory perceptions of the body.
5. This changed view will bring about a diagnostic reclassification and redefinition of CRPS, will lead to new mechanism-based therapeutic approaches, and will shift the focus of our research efforts.

Fig. 19 Development of CRPS as disease of the central nervous system: a hypothesis. Schematic diagram summarizing the sensory, autonomic and somatomotor changes in CRPS I patients. The figure symbolizes the CNS (forebrain, brain stem and spinal cord). Changes occur in the central representations of the somatosensory, somatomotor and sympathetic nervous system (which include spinal circuits) and are reflected in the changes of perception of painful and non-painful stimuli, of cutaneous blood flow and sweating, and of motor performances. They are triggered and possibly maintained by nociceptive afferent inputs from the somatic and visceral body domains. It is unclear whether these central changes are reversible in chronic CRPS I patients. The central changes affect the endogenous control system of nociceptive impulse transmission possibly too. Coupling between sympathetic neurons and afferent neurons in the periphery (see bold closed arrow) is one component of pain in CRPS I patients with SMP. However, it seems to be unimportant in CRPS I patients without SMP. Modified from [9,10].

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Complex Regional Pain Syndrome

Type I (previously reflex sympathetic dystrophy)
Type II (previously causalgia)

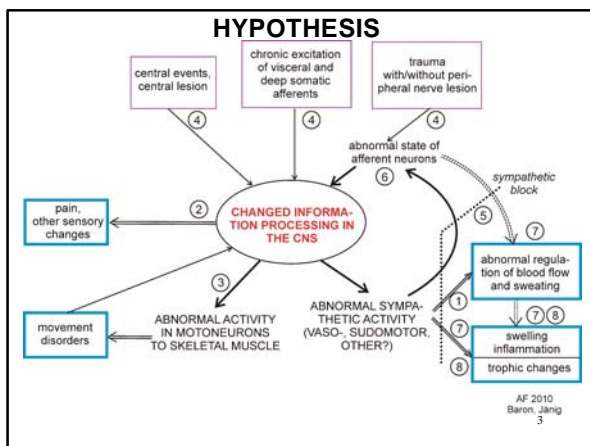
Central Changes

1. Changes of regulation by sympathetic systems
2. Sensory changes
3. Somatomotor changes
4. Initiating events
5. Pain relief by sympathetic blocks with local anesthetics

Peripheral Changes

6. Sympathetic-afferent coupling
7. Inflammatory changes and edema
8. Trophic changes

2

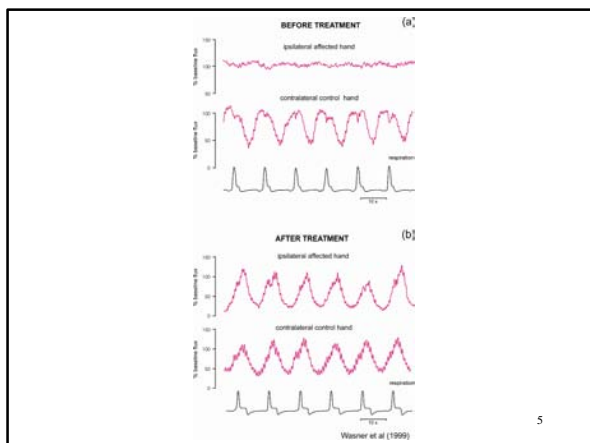


Arguments in favor of *CENTRAL* changes occurring in CRPS I

1. **Changes of regulation by sympathetic systems**
 - n Thermoregulatory reflexes in CVC neurons reduced
 - n Respiration elicited reflexes (deep in- and expiration) in CVC reduced
 - n Changes of sweating in SM neurons
 - n (Swelling reduced by sympathetic blocks)
2. Sensory changes
3. Somatomotor changes
4. Initiating events
5. Pain relief by sympathetic blocks with local anesthetics

CVC cutaneous vasoconstrictor
SM sudomotor

4

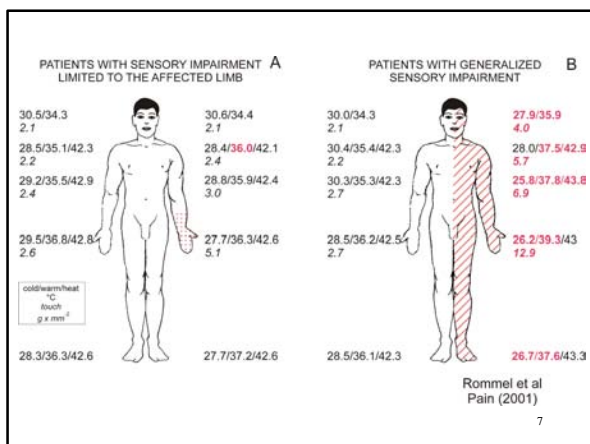


5

Arguments in favor of *CENTRAL* changes occurring in CRPS I

1. Changes of regulation by sympathetic systems
2. **Sensory changes**
 - n Mechanical allodynia (quadrant, hemisensory)
 - n Hypoesthesia (mechanical, cold, warm; hemisensory, quadrant)
3. Somatomotor changes
4. Initiating events
5. Pain relief by sympathetic blocks with local anesthetics:

6



Arguments in favor of CENTRAL changes occurring in CRPS I

- Changes of regulation by sympathetic systems
- Sensory changes
- Somatomotor changes**
 - Active range of motion reduced
 - Physiological tremor increased
 - Dystonia
 - Active motor force reduced
- Initiating events
- Pain relief by sympathetic blocks with local anesthetics:

8

Arguments in favor of CENTRAL changes occurring in CRPS I

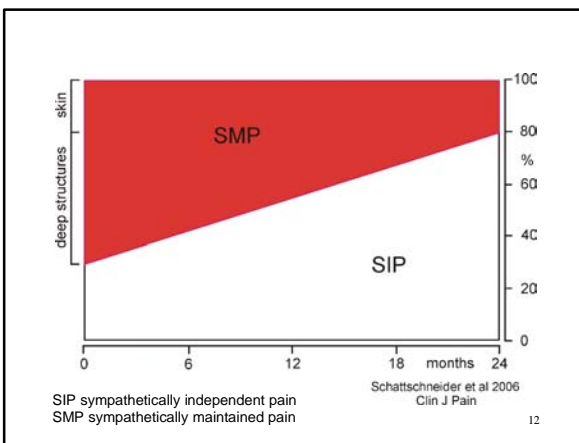
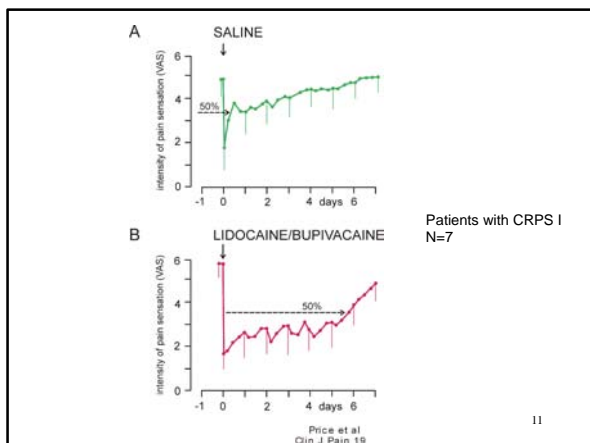
- Changes of regulation by sympathetic systems
- Sensory changes
- Somatomotor changes
- Initiating events**
 - Out of proportion to pain disease (minor trauma)
 - Events remote from affected extremity (e.g., in visceral domain)
 - Central (related to endogenous control systems?)
- Pain relief by sympathetic blocks with local anesthetics

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Arguments in favor of CENTRAL changes occurring in CRPS I

- Changes of regulation by sympathetic systems
- Sensory changes
- Somatomotor changes
- Initiating events
- Pain relief by sympathetic blocks with local anesthetics:**
 - Relief of pain outlasts conduction block by an order of magnitude, i.e. a temporary block is followed by a long-lasting pain relief
 - A few temporary blocks are sometimes sufficient to generate permanent pain relief
 - Sympathetic activity maintains a positive feedback circuit (?)

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Arguments in favor of PERIPHERAL changes occurring in CRPS

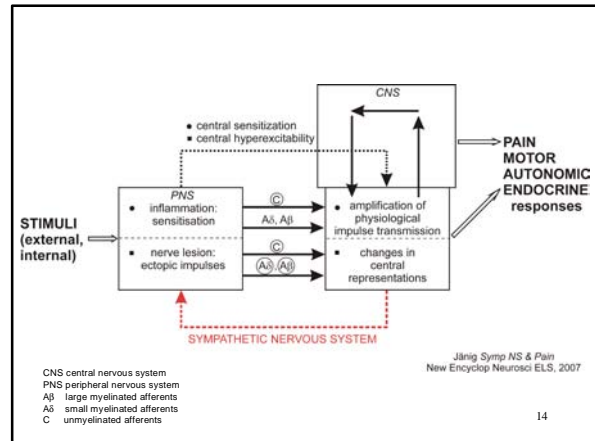
6. Sympathetic-afferent coupling

- n After nerve lesion via norepinephrine and adrenoceptors (CRPS II)
- n Indirectly via vascular bed and other mechanisms (CRPS I; deep somatic?)
- n [Indirectly via inflammatory mediators and neurotrophic factors]
- n [Mediated by the adrenal medulla (epinephrine)]

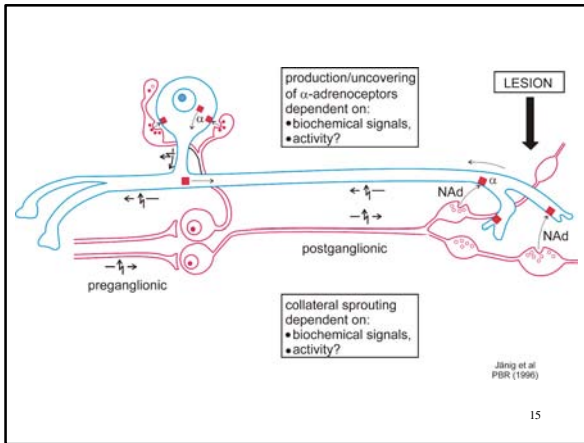
7. Inflammatory changes and edema

8. Trophic changes

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Arguments in favor of PERIPHERAL changes occurring in CRPS

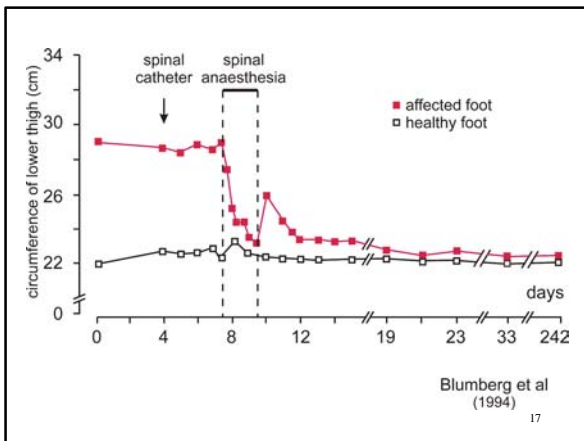
6. Sympathetic-afferent coupling

7. Inflammatory changes and edema

- n Neurogenic inflammation (precapillary vasodilation, venular plasma extravasation), involvement of peptidergic afferents (?)
- n Sympathetic fibers mediating effects of inflammatory mediators (e.g., bradykinin) to venules leading to plasma extravasation (?)
- n Involvement of inflammatory cells and immune system (?)
- n Change of capillary filtration pressure (?)

8. Trophic changes

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Arguments in favor of PERIPHERAL changes occurring in CRPS

6. Sympathetic-afferent coupling

7. Inflammatory changes and edema

8. Trophic changes

- n Long-range consequences of inflammatory changes and edema (?)
- n Direct (trophic?) effect of sympathetic and afferent fibers on tissue (?)

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