



Review

Forty years in capsaicin research for sensory pharmacology and physiology

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Abstract

Capsaicin, the pungent ingredient of chilli peppers has become a “hot” topic in neuroscience with yearly publications over half thousand papers. It is outlined in this survey how this exciting Hungarian research field emerged from almost complete ignorance. From the initial observation of the phenomenon of “capsaicin desensitization”, a long-lasting chemoanalgesia and impairment in thermoregulation against heat, the chain of new discoveries which led to the formulation of the existence of a “capsaicin receptor” on C-polymodal nociceptors is briefly summarized. Neurogenic inflammation is mediated by these C-afferents which are supplied by the putative capsaicin receptor and were termed as “capsaicin sensitive” chemoceptive afferents. They opened new avenues in local peptidergic regulation in peripheral tissues. It has been suggested that in contrast to the classical axon reflex theory, the capsaicin-sensitive sensory system subserves a “dual sensory-efferent” function whereby initiation of afferent signals and neuropeptide release are coupled at the same nerve endings. Furthermore, in the skin at threshold stimuli which do not evoke sensation elicit already maximum efferent response as enhanced microcirculation. In isolated organ preparations large scale of new type of peptidergic capsaicin-sensitive neurogenic smooth muscle responses were revealed after the first one was described by ourselves on the guinea-pig ileum in 1978. Recently the “capsaicin receptor” has been cloned and it is now named as the “transient receptor potential vanilloid 1” (TRPV1). Hence, capsaicin research led to the discovery of the first temperature-gated ion channel gated by noxious heat, protons, vanilloids and endogenous ligands as anandamide, *N*-oleoyldopamine and lipoxygenase products. Another recent achievement is the discovery of a novel “unorthodox” neurohumoral regulatory mechanism mediated by somatostatin. Somatostatin released from the TRPV1-expressing nerve endings reaches the circulation and elicits systemic antiinflammatory and analgesic “sensocrine” functions with counter-regulatory influence e.g. in Freund’s adjuvant-induced chronic arthritis. Nociceptors supplied by TRPV1 and *sst4* somatostatin receptors has become nowadays promising targets for drug development.

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1. Introduction

The steeply increasing number of publications on capsaicin exceeding 650–700 papers per year is a clear indication that this spicy pungent agent has become nowadays really a “hot” topic in neuroscience. In striking contrast during my fifteen year long “first capsaicin period” (1962–1976) altogether less than 40 papers were published from non-Hungarian sources and very few of them were related to neurobiology in its broadest sense. There are two reasons why the emerging interest is nowadays so high. First, in drug research capsaicin and its receptor have become generally accepted lead and target molecules, respectively. The promising perspective of this trend is to discover the first analgesic and antiinflammatory drug which acts not on cyclooxygenases or opioid receptors but selectively on nociceptors. The second reason is related to the new horizons of the neurohumoral regulatory role of mediators (neuropeptides) released from capsaicin-sensitive nociceptors. It is somehow rewarding for me that in the late sixties just these two reasons – what I formulated in my thesis, early publications and reviews – inspired me to devote all my scientific efforts with limited facilities to break through several burdens in this pathway (Szolcsányi, 1982, 1984a,b, 1990, 1991, 1993, 1996a,b, 2002; Szolcsányi et al., 1994, 2004).

2. Capsaicin desensitization and neurogenic inflammation

Nicholas (Miklós) Jancsó, my mentor with whom I worked together in Szeged until his demise in 1966, discovered around the late forties as an accidental observation that high doses of capsaicin applied topically or later also systemically to mice, rats or guinea-pigs elicit a novel type of analgesia. The so called capsaicin desensitized animals did not react with protective reflexes and inflammation to noxious chemicals although their responsiveness to physical stimuli remained intact (Szolcsányi, 1982, 1984a). It was my good fortune that I came

into his department with some neurophysiological background and he involved me in his capsaicin research that he was conducting with his wife Aurelia (Aranka) Jancsó-Gábor. The first paper in a well-recognized refereed journal on capsaicin desensitization and on the direct evidence for the existence of neurogenic inflammation was sent for publication one year after N. Jancsó left us (Jancsó et al., 1967). Although phenomena of antidromic vasodilatation and axon reflex flare were known for several decades, venular plasma extravasation being the cardinal initial event of inflammation was not shown previously in response to electrical nerve stimulation. Furthermore, the response was absent in capsaicin desensitized animals indicating that the mediator is released from chemonociceptive nerve endings. Neurogenic inflammation together with the interest in capsaicin, however, remained abandoned by the rest of the world until the late seventies (Holzer, 1991; Maggi, 1995; Szolcsányi, 1996a).

3. Actions of capsaicin on thermoregulation

Systemic application of capsaicin or its pungent congeners elicited a pronounced fall in body temperature and this response was also absent in capsaicin desensitized animals. The hypothermic effect of the agent was due to a coordinated heat loss response accompanied by vasodilatation, salivation, fall in metabolic rate at cool ambient temperature and in cats also by panting. Heat loss responses to heating the preoptic area or to intrahypothalamic microinjection of capsaicin were also diminished in these capsaicin pretreated animals. Remarkably this state of unresponsiveness lasted for months and was accompanied by mitochondrial swelling both in B-type neurons of trigeminal and dorsal root ganglia, as well in small type neurons of the preoptic area (Szolcsányi, 1982; Szolcsányi et al., 1971; Szolcsányi and Jancsó-Gábor, 1975a). Fig. 1 shows that heat escape behaviour from a warm environment is absent in these capsaicin pretreated rats, while under the acute

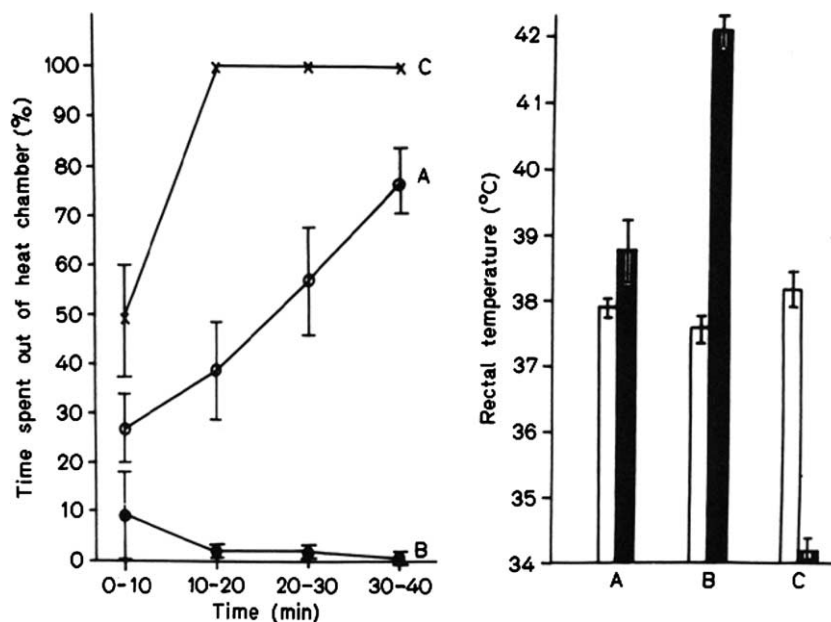


Fig. 1. Escape reaction of rats from a heat chamber (39–41 °C) measured over 10 min periods, and their rectal temperature before (white columns) and after (black columns) exposure. (a) Normal controls ($n = 11$); (b) rats desensitized by 150 mg/kg s.c. capsaicin 20 days before the experiment ($n = 11$); (c) rats treated with capsaicin (1 mg/kg s.c.) 10 min before the experiment ($n = 5$). (Reproduced by the kind permission of S. Karger AG, from Szolcsányi and Jancsó-Gábor (1975a) with permission.)

effect of capsaicin the pronounced fall in body temperature is accompanied by complete avoidance of the warm environment. These functional and ultrastructural findings provided the first evidence for an action of capsaicin in the central nervous system and indicated that both the central and peripheral warmth sensors are stimulated and desensitized against their natural stimuli.

4. Postulation of a capsaicin receptor on polymodal nociceptors

The uniqueness of these pharmacological effects of capsaicin was challenging for further research, but the mechanism behind the extremely long-term capsaicin-induced blockade of chemonociception against such diverse structures as xylene, formaldehyde, veratridine or mustard oil remained enigmatic and seemed to favour some kind of neurotoxicity. Beyond the selective ultrastructural impairment restricted to one set of neurons mentioned before (Szolcsányi et al., 1975), results of three sets of tests convinced me about its promising perspectives in drug research. (1) Frogs and birds were completely insensitive to capsaicin and putting frogs into a 1% capsaicin solution for weeks did not induce behavioural changes, toxicity or desensitization against chemical stimuli (Jancsó et al., 1967). (2) **Desensitizing our tongue by 10 times 1 min application of 1% capsaicin solution impaired only the pungent effects of capsaicin, piperine, mustard oil and zingerone but not the taste or menthol-induced cool sensations. Furthermore, cold**

and tactile discrimination limens remained also intact in contrast to discrimination in the warm range. These changes were reversible after one day (Szolcsányi, 1977). (3) Structure–activity relationships of capsaicin congeners in respect of the stimulatory and desensitizing effects using the wiping test in the rat revealed that the nociceptive effect of the compounds is not proportional to the desensitizing effect and their ratio spans from 1:1 to 1400:1 (Szolcsányi and Jancsó-Gábor, 1976). On the basis of all these results the hypothesis for the existence of a “capsaicin receptor” in the lipoprotein membrane has been put forward (Szolcsányi and Jancsó-Gábor, 1975b). Fig. 2 shows the pharmacophores and possible multiple interactions of capsaicin with its putative receptor molecule. In the chemoanalgesic effect of capsaicin type agents a sensory neuron blocking action and not a desensitization of the capsaicin receptor was proposed, since: (1) the effects of chemically unrelated compounds were also abolished; (2) the neurogenic inflammation evoked by electrical nerve stimulation was also absent in these capsaicin pretreated animals; and (3) topical application induced ultrastructural changes in the corneal nerve endings (Szolcsányi et al., 1975). The first electrophysiological evidence that these capsaicin-sensitive nerve endings are the C-polymodal nociceptors was reported in 1974–77 (Szolcsányi, 1977). Subsequently, single unit recordings from the great auricle nerve of the rabbit that I made in Ed Perl’s laboratories during a sabbatical year of 1977–78 provided direct evidence for the highly selective stimulatory and desensitizing effects of capsaicin on C-polymodal nociceptors.

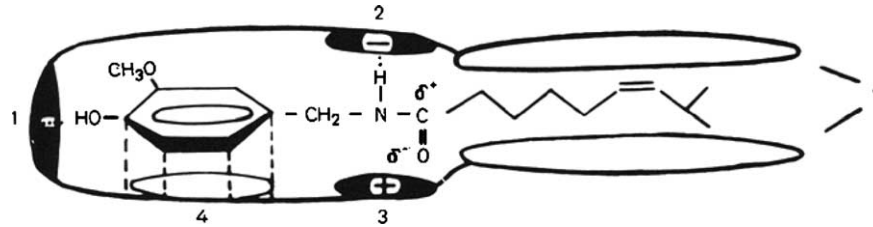


Fig. 2. Schematic representation of the hypothetical capsaicin receptor. (1) H-bonding site for the OH group; (2) electronegative site for the H of the NH group and for the +C atom; (3) electropositive site for oxygen of the carbonyl group; (4 and 5) apolar areas bound by van der Waal's forces. (Reproduced by the kind permission of Editio Cantor Verlag from Szolcsányi and Jancsó-Gábor (1975b) with permission.)

Furthermore, clear evidence was obtained, that after close arterial injection the transduction processes are desensitized to their natural stimuli without degeneration or blockade of axonal conduction (Szolcsányi, 1982, 1984b, 1987, 1993). Fig. 3 shows the desensitizing effect of $5 \times 200 \mu\text{g}$ plus $5 \times 600 \mu\text{g}$ capsaicin on responses of single C-polymodal nociceptors to thermal stimuli and bradykinin. In the neonatal rat the irreversible loss of mainly B-type neurons and C-afferent fibers is not due to acute neurotoxic cell death (Jancsó et al., 1977), but to a late response of impaired uptake of NGF from the damaged nerve terminals. The loss of neurons was prevented by NGF after-treatment (Szöke et al., 2002).

5. Dual sensory-efferent function of capsaicin-sensitive nociceptors

Our proposal of “dual sensory-efferent function” for a nerve ending is against the classical works of Bayliss, Bruce and Thomas Lewis on antidromic vasodilatation

and axon reflex flare. According to the views of these pioneers signals from sensors are conducted through axonal arborization to nerve terminals specialized for mediator releasing functions (Szolcsányi, 1984b, 1988, 1996a,b). Taking the advantage of the neuroselective action of capsaicin we showed that blockade of axonal conduction by local anaesthetics or tetrodotoxin did not inhibit neurogenic inflammation or the release of sensory, neuropeptides, although they were absent after chronic sensory denervation. Thus, spike generation at the capsaicin-sensitive sensors is coupled at the same ending with a neuropeptide release (Fig. 4). According to our “reevaluation of axon reflex theory” (Szolcsányi, 1988, 1996a), terminal axonal arborizations of these nerves form varicosities, suitable for dual sensory-efferent functions at all ends of the axon reflex arc.

New horizons for the sensory-efferent function of capsaicin-sensitive nerve terminals were revealed in isolated organ preparations. On the classical preparation of the guinea-pig isolated ileum Loránd Barthó and myself provided the first in vitro evidence both for the neuroselective action of capsaicin and for a novel type of

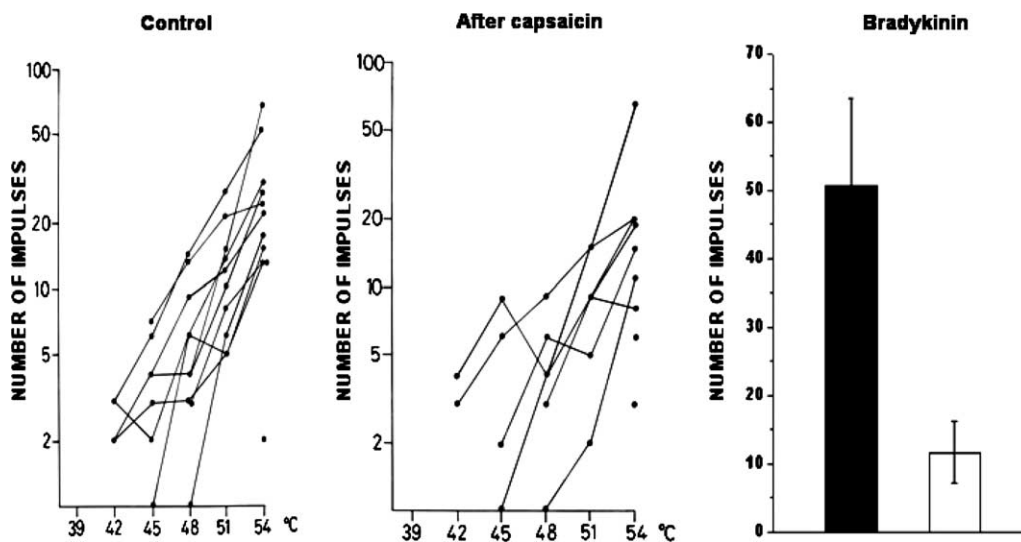


Fig. 3. Single unit discharges of C-polymodal nociceptors recorded from the great auricle nerve of rabbits ($n = 11$) evoked by six steps 17s local heating of the receptive field (Control) or to close arterial injection of $0.2 \mu\text{g}$ bradykinin (black column $\times \pm$ SE). Discharges of the same units several minutes (more than 15 min) after $5 \times 200 \mu\text{g}$ plus $5 \times 600 \mu\text{g}$ i.a. injections of capsaicin (After capsaicin and white column). Levels of significance in differences of means are: at $48 \text{ }^\circ\text{C}$ $p < 0.05$, at $51 \text{ }^\circ\text{C}$, $54 \text{ }^\circ\text{C}$ and bradykinin $p < 0.01$ (unpublished details from Szolcsányi (1987)).

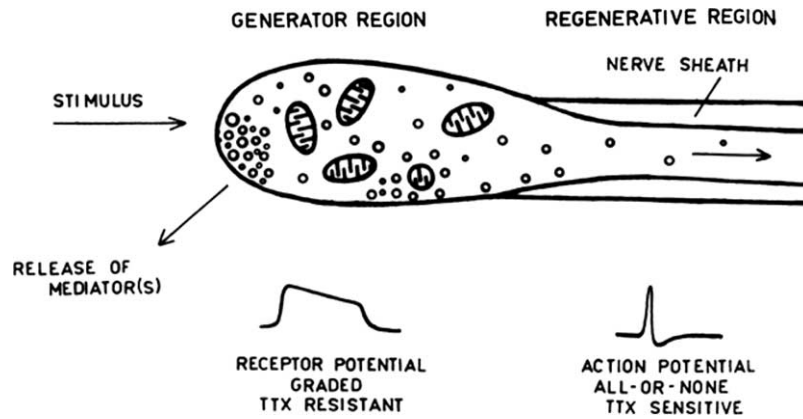


Fig. 4. Theory of dual sensory-efferent function of capsaicin-sensitive nociceptors. (Reproduced by the kind permission of Birkhäuser (Verlag) Publishing House from Szolcsányi (1988).)

neural smooth muscle response mediated by capsaicin-sensitive sensory nerve terminals (Szolcsányi and Barthó, 1978). At that time my single unit studies revealed already the highly selective action of capsaicin on cutaneous C-polymodal nociceptors, therefore for labeling these neural responses mediated by physiologically unclassified fibers which are apparently supplied by the putative capsaicin receptor, the term “capsaicin-sensitive” afferents was introduced (Szolcsányi and Barthó, 1978, 1979). Similar new type of capsaicin-sensitive neural response was subsequently discovered in the trachea and bronchi of the guinea-pig (Szolcsányi and Barthó, 1982). Fig. 5 shows that field stimulation of the main bronchi which activated all neural elements in the tissue elicited much more pronounced capsaicin-sensitive contractions than that mediated by cholinergic parasympathetic fibers. The impact of these studies was

fast and immense and in various in vitro organs several similar neural responses mediated by tachykinins and CGRP were described (Holzer, 1991; Maggi, 1995).

In collaboration with the group of Fred Lembeck from Graz the mediator role of substance P in the capsaicin-sensitive neural contraction of the guinea-pig ileum was identified and in cooperation with Tony Yaksh depletion and release of neuropeptides in the spinal cord to capsaicin congeners were reported (Holzer, 1991). Nevertheless, our group during the eighties and early nineties owing to the lack of radioimmunoassay and immunohistochemical techniques could not participate in the highly productive race for discovering the role of different neuropeptides in capsaicin-mediated responses. Instead, we described that antidromic dorsal root stimulation with 1–2 pulses and at extremely low frequency (e.g. 0.1 Hz) which stimulate C-polymodal nociceptors without evoking pain or any sensation was already highly effective to evoke enhancement in cutaneous microcirculation (Szolcsányi, 1988, 1991; Szolcsányi et al., 1992, 2004). The hypothesis was put forward that the capsaicin-sensitive neuronal population which comprises about 50% of the total number of sensory neurons of the dorsal root and trigeminal ganglia subserves at threshold stimuli local efferent function without causing pain. Stronger stimuli e.g. which elicit 2Hz frequency of discharges are needed for evoking nociception, pain and neurogenic inflammation. Thus, the capsaicin-sensitive sensory neural system – or at least a substantial part of it – is functionally distinct from the classical sensory and autonomic divisions of the peripheral nervous system. This suggestion is in contrast to the accepted views held since the Cartesian reflex principle had been formulated. As an example for the regulatory role of these mechanisms, a protective effect of capsaicin-sensitive nerve endings in the gastric mucosa of the rat was shown by Loránd Barthó and myself and was analysed later in detail by Peter Holzer (Holzer, 1991; Maggi, 1995; Szolcsányi, 1984b, 1996b).

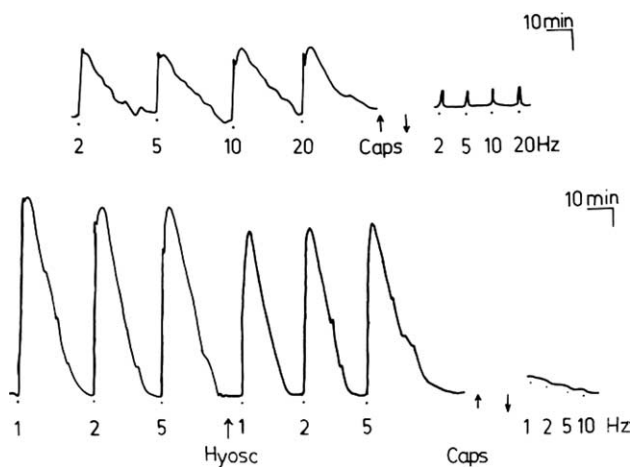


Fig. 5. Contractions of the isolated main bronchi of the guinea-pig to field stimulation (40V, 0.1 ms, 100 pulses, frequencies as indicated). Caps: 10 min exposure to capsaicin (3.3 μ M) followed by a 60 min resting period. Hyosc: hyoscine (3 μ M). Vertical calibrations correspond to one-tenth of maximum contraction of the tissue. (Reproduced by the kind permission Elsevier Ireland Publishing House from Szolcsányi and Barthó (1982).)

6. The TRPV1/VR1 capsaicin receptor

From the late eighties conclusive evidence has accumulated for the existence of a capsaicin receptor and a novel capsaicin-gated cation channel was identified in patch clamp studies (Bevan and Szolcsányi, 1990). Thus, strong efforts were made to isolate, identify and clone this membrane protein. Finally, it was succeeded by the group of David Julius in 1997 (Caterina et al., 1997). It was named by the authors both as “capsaicin receptor” or as “vanilloid receptor 1” (VR1) and recently renamed by the IUPHAR Nomenclature Committee on the basis of structural analogies to the “transient receptor potential vanilloid 1” (TRPV1). This at that time unique noxious heat-gated ion channel is gated also by protons beyond vanilloids as capsaicin and resiniferatoxin (Szallási and Blumberg, 1999; Szolcsányi, 2002; Gunthorpe et al., 2002). For the endogenous chemical ligand anandamide or lipoxygenase products were proposed, but the issue is not yet settled. According to our recent findings *N*-oleoyldopamine or its structural derivatives might also be putative endogenous ligands of the TRPV1 capsaicin receptor (Szolcsányi et al., 2004), since it has less counteracting cannabinoid receptor agonist effect than anandamide and other arachidonylamides (Szolcsányi, 2002).

7. Sensocrine function of capsaicin-sensitive nociceptors

It was serendipity, an unexpected observation made by my coworker Erika Pintér that in the course of rat experiments for mapping neurogenic inflammation in visceral organs by antidromic stimulation of dorsal roots, the cutaneous blueing response to the first stimulation was obviously more pronounced than the effect evoked by a subsequent stimulation of another pair of dorsal roots (Pintér and Szolcsányi, 1995, 1996). Thus, the paradigm was changed and only single stimulation was performed in each rat which enabled us to describe the lumbosacral segmental territorial innervations of sensory neurons having capsaicin-sensitive nerve terminals with dual sensory-efferent functions (Pintér and Szolcsányi, 1995). The intriguing first phenomenon was afterwards analysed further (Szolcsányi et al., 1998, 2004), since it clearly indicated that from these sensory nerve endings some mediator is released which elicits inhibition outside the innervation area. Several experimental paradigms were applied and it turned out that antidromic stimulation of the lumbosacral dorsal roots on one side induced around a 50% inhibition of neurogenic inflammation on the other side. Effects of capsaicin, sciatic nerve stimulation, or carrageenin subplantar injections all were inhibited. Similar inhibition was achieved on the contralateral side when peripheral stump of cut sciatic nerve was stimulated under the ef-

fect of pipercuronium, guanethidine and atropine on vagal or sciatic nerve stimulation. Perineural application of capsaicin prevented these antiinflammatory effects, but adrenalectomy did not inhibit them. Furthermore, orthodromic stimulation of these capsaicin-sensitive nociceptors by mustard oil in the acutely denervated hindleg inhibited also the inflammation evoked by mustard oil or carrageenin in the contralateral hindpaw. Vagal nerve stimulation was also effective to elicit a systemic antiinflammatory response. Fig. 6 shows that contralateral antidromic stimulation of the sensory nerves in the sciatic nerve inhibits both the effect of antidromic nerve stimulation (a) and also the inflammatory effect of carrageenin ((b) and (c)). Particularly interesting was that 0.1 Hz stimulation did not evoke plasma extravasation in the innervated area, but still markedly inhibited the carrageenin oedema in the contralateral paw. This finding among others indicated that the mediator with systemic antiinflammatory effect is not released from the inflammatory exudate (Fig. 6(c)).

Fourfold increase in plasma somatostatin-like immunoreactivity to sciatic nerve stimulation or mustard oil application was found and the systemic antiinflammatory effect of these sensory stimulations were completely absent in rats pretreated with polyclonal somatostatin antibody or by a somatostatin depleting agent, cysteamine. Therefore, it has been suggested that the systemic antiinflammatory – and also as detected analgesic-effect which develops in response to noxious or nonnoxious level of stimulation of capsaicin-sensitive nociceptors is due to a release of somatostatin from them. This release process, site and function of somatostatin are different from the well-known endocrine, paracrine and neuro-

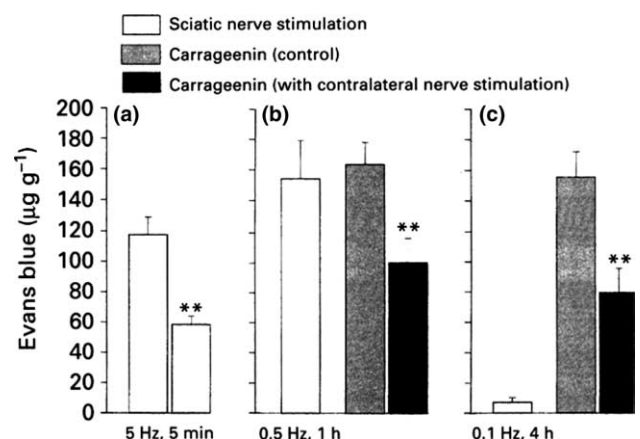


Fig. 6. Plasma extravasation in the skin of the hindpaw in anaesthetized rats pretreated with guanethidine (8 mg/kg i.p.) and pipercuronium (200 µg/kg i.v.) after artificial respiration. (a) First column shows the effect of stimulation of the right paw, the second column the effect of subsequent (5 min) stimulation of the left paw; (b and c) subplantar injection of carrageenin (1% 100 µl) was given when the contralateral sciatic nerve stimulation started. (Reproduced by the kind permission of Stockon Press Co., from Szolcsányi et al. (1998) with permission.)

transmitter roles described for this neuropeptide earlier. Therefore, to label this novel neurohumoral regulatory mechanism, the term “sensocrine” function of capsaicin-sensitive nociceptors was introduced (Szolcsányi et al., 2004). In addition to the “local sensory-efferent” role of capsaicin-sensitive, TRPV1-expressing substantial portion of the primary afferent neuron population, this “unorthodox” systemic endocrine-like “sensocrine function” is a conceptually highly interesting new scope within the spectrum of neurohumoral regulatory mechanisms. Pathophysiological counter-regulatory role of this novel system has been found in Freund’s adjuvant-induced arthritis model (Helyes et al., 2004) and in experimental diabetes (Pórszász et al., 2003). Furthermore, this concept seems to have also a promising practical outcome for drug development. The stable somatostatin analogue TT-232 which is devoid of the endocrine effects of its parent hormone due to its highest affinity to sst4 receptors proved to be a potent anti-inflammatory and analgesic compound. In contrast to the cyclooxygenase inhibitors it diminishes the neurogenic inflammation and could markedly protect against the cartilage and bone destruction in Freund’s adjuvant-induced chronic arthritis model of rheumatoid arthritis (Helyes et al., 2004).



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