Summary

Capsaicin, the most pungent ingredient in red peppers, has been used for centuries to remedy pain. Recently, its role has come under reinvestigation due to evidence that the drug acts selectively on a subpopulation of primary sensory neurons with a nociceptive function. These neurons, besides generating pain sensations, participate through an antidromic activation in the process known as neurogenic inflammation. The first exposure to capsaicin intensely activates these neurons in both senses (orthodromic: pain sensation; antidromic: local reddening, oedema etc.). After the first exposure, the neurons become insensitive to all further stimulation (including capsaicin itself). This evidence led to the proposal of capsaicin as a prototype of an agent producing selective analgesia. This perspective is radically different from previous 'folk medicine' cures, where the drug was used as a counter-irritating agent (i.e. for muscular pain). The new concept requires that capsaicin be repeatedly applied on the painful area to obtain the desensitisation of the sensory neurons. Following this idea, capsaicin has been used successfully in controlling pain in postherpetic neuralgia, diabetic neuropathy and other conditions of neuropathic pain. Furthermore, evidence indicates that capsaicin could also control the pain of osteoarthritis. Finally, repeated applications of the drug to the nasal mucosa result in the prevention of cluster headache attacks. On the basis of this evidence, capsaicin appears to be a promising prototype for obtaining selective analgesia in localised pain syndromes.

Capsaicin is the most pungent ingredient among those present in the red pepper. In consideration of its peculiar and diverse biological effects, the red pepper has been used throughout history not only as a precious ingredient for flavouring food, but also as an instrument for particular rituals and as a medicine to cure symptoms such as pain, itching and even constipation.

In recent years, a great interest also has developed towards capsaicin as an effective instrument in biomedical research. The scientific interest in this pharmaceutical compound is motivated by the fact that capsaicin exerts a peculiar action on a subpopulation of sensory neurons with a possible nociceptive action. Evidence of the chief physiological role played by this subpopulation of peripheral sensory neurons has increased this interest. Much attention has been given to the fact that these peripheral sensory neurons (type-C unmyelinated fibres) are capable of synthesising and releasing certain neuropeptides such as substance-P, neurokinin-A and the calcitonin gene-related peptide (CGRP). The function of this subpopulation of sensitive primary neurons is primarily that of conducting pain.
generated by some particular stimuli (especially those originating from thermal or chemical mechanisms).\[2\] Furthermore, besides being activated in a centripetal (orthodromic) sense, these fibres could be also activated in a centrifugal (antidromic) sense, discharging neuropeptides to the periphery. Through this action, the fibres participate in the phenomena which constitute the initial response of the organism to noxious stimuli which may damage its integrity.\[3\] Following this profile, these sensitive neurons would be the agents of the so-called ‘nocifensor system’, hypothesised by Lewis in the 1920s, and could be the primum movens of neurogenic inflammation.\[4\]

1. Mechanism of Capsaicin Action

A characteristic of capsaicin is the selective and highly specific activation of the above-described fibres.\[5\] In particular, capsaicin induces an intense activation upon first contact with these fibres, as intense as the initiation and the conduction of painful signals towards the central structure.\[6\] The activation of the nociceptive fibres induces a release of excitatory neurotransmitters, such as tachykinin (particularly substance-P) or N-methyl-D-aspartic acid (NMDA), which promotes the activation of the nociceptive pathways at the central level.\[7\] As mentioned, it has been demonstrated that capsaicin is capable of inducing an antidromic activation of these fibres which elicits the release of neuropeptides from the peripheral terminals.\[8\] The centripetal barrage of sensory neurons and the peripheral release of neuropeptides are among the phenomena that have been demonstrated as being present in various tissues of experimental animals.\[9,10\]

Particular mention should be made of the viscerogenetic effects of capsaicin (obviously through the induced release of neuropeptides). It has been demonstrated that organs such as the bladder and the stomach\[9,10\] respond with variations of calibre or functioning to the exposure to capsaicin. These results clearly indicate how the neurons, which are sensitive to capsaicin, participate in the physiological mechanism of regulating visceral motility and how they could play an active role in efferent components of visceral reflexes. There is evidence in vivo that corresponds to what has been found in vitro.

In humans, easily verifiable proof of the acute effect of capsaicin is the burning sensation which is induced by contact with the red pepper. Similarly, the reddening, oedema and the vasodilation present at the same time on exposed skin (or mucosa) are an indication of an antidromic activation. However, the effect of capsaicin is not limited to intense activation during the first application. The substance, after the first direct contact, is capable of inducing a lasting block on the sensitivity and activity of the sensitive fibres. In fact, after the first contact with capsaicin, the fibres are no longer activated by capsaicin itself or by other stimuli usually capable of activating them.\[11\] The tachyphylaxis of the capsaicin effect is observable in all models that have been described previously (stomach, bladder, visceral reflexes, etc.). Thus, the centripetal barrage measured during the first exposure to the drug through neurophysiological methods is not present during successive exposures.\[11\] An analogous block exists with the release of peripheral neuropeptides.\[12\]

The specificity of the capsaicin biological effect suggests the existence of specific sites where the drug exerts its pharmacological action. Jancso\[11\] postulated the existence of capsaicin-sensitive ‘pain receptors’. This expression only indicated the possibility of a specific site of action without identifying the nature of the same site. During the past 2 decades the hypothetical receptors of capsaicin (and the possible endogenous capsacinoids) have been sought. The methods, utilising radiolabelled capsaicin or capsaicin-like photoaffinity, failed to identify the pharmacological receptor. The use of resiniferotoxin, a more potent capsaicin analogue isolated from Euphorbia resinifera, led to the identification of the capsaicin receptor.\[12\] The activation of this receptor opens the cation channel (particularly Ca\(^{++}\)) of the cellular membrane. This cation influx generates the excitatory impulse (or the peripheral release of the neuromediator).\[13\]