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Red pepper: an aid for gut functional diseases with pain?

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Functional dyspepsia and irritable bowel syndrome (IBS), as well as other gut functional diseases characterized by visceral hypersensitivity and pain, may render quality of life very poor and account for about 1/3 of visits to gastroenterology departments. They also represent a high cost for society in terms of prescriptions and sick leave. Following an emerging trend some attempts have been made to pharmacologically decrease visceral hypersensitivity with a number of drugs, but with little clinical success. In recent years, however, visceral hypersensitivity and pain have been ascribed in most cases to hyperactivity of transient receptor potential vanilloid 1 ($TRPV_1$) nociceptive fibers, that transfer the pain sensations to central nervous system (CNS), which are activated by noxious thermal, mechanical or chemical stimuli and these may be a new target for treatment of visceral pain [1].

Red pepper has been used for many years, transdermally to alleviate osteoarticular and neuropathic pain and its analgesic property is connected to its content in capsaicin, a transient stimulator of $TRPV_1$ fibers (sensitization), which locks their neuronal membrane in a depolarized state that prevents subsequent depolarization, with consequent decrease of pain sensation (desensitization). Until about ten years ago the analgesic effect of capsaicin was exploited only through cutaneous application to reach the $TRPV_1$ of the somatic nociceptive nerves.

The novel idea was to reach the $TRPV_1$ of the gastrointestinal nociceptive fibers by ingesting red pepper and was described for the first time in a study of the effect of red pepper on painful symptoms of functional dyspepsia in 2002 [2]. In fact the epigastric pain of patients who ingested a daily amount of 2.5 g of red pepper containing 0.7 mg/g of capsaicin for five weeks, started to significantly decrease after three weeks with respect both to basal period and to patients who received placebo randomly and in a double blind manner. This paper represented the first clinical application of TRPV1 channel desensitization to treat visceral pain. Subsequently, because an increase in $TRPV_1$ nerve fibers was found in colonic mucosa of IBS patients that was correlated with pain [3], a double blind controlled study on the effect of red pepper in these patients was carried out by administering red pepper enteric-coated pills, which demonstrated a significant improvement in abdominal pain after five weeks [4]. Although these results suggest a novel way of dealing with these frequent and distressing functional diseases, this approach was not clinically put into practice. One reason may be that the analgesic effect of red pepper is obtained at the expense of an initial, although transitory, exacerbation of pain in the first weeks of treatment in some patients [2,4].

Perhaps gastroenterologists are waiting for $TRPV_1$ antagonists that, instead of desensitizing TRPV1, directly block its activation [5]. This way, however, is more risky, because $TRPV_1$ is expressed not only in visceral neurons, but also in the CNS and in non-neuronal cells, where it is involved in many other important physiological functions of the body [6]. The appearance of serious side effects with these $TRPV_1$ antagonists, such as hyperthermia and insensitivity to noxious heat, has prevented their experimentation in man. Desensitization of $TRPV_1$ receptors through capsaicin administration is surely less dangerous than $TRPV_1$ blockers; because red pepper is recognized as safe by the FDA for oral use, and millions of persons in the world, especially in south-east Asia, consume large quantities of capsaicin with red pepper (2.5-8 g/person) every day for life without evident adverse consequences. On the contrary, a beneficial effect on functional gut diseases may be inferred considering that these functional diseases, and in particular IBS, have a markedly lower prevalence in these countries than in western countries [7]. For these reasons the use of capsaicin should be promoted in the clinical management of this kind of visceral pain, including pain due to esophageal and rectal hypersensitivity, at least until $TRPV_1$ antagonists have reached a level of safety.

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