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Response to Szolcsányi

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We thank Professor Szolcsanyi for carefully reading our review and for his insightful comment about neuroregulation of the cutaneous microcirculation. We acknowledge that the figure schematizing the pathways underlying local thermal hyperemia in the skin may be partly inaccurate. However, we would like to emphasize that neuroregulation of the initial rise in skin blood flow following local heating remains a rather 'grey' area. This initial vasodilation has been commonly (improperly?) referred to as initial 'axon reflex' since the pivotal work by Minson and colleagues, who showed that antebrachial cutaneous nerve block with bupivacaine before local heating does not alter the response, whereas application of lidocaine/prilocaine cream reduces the peak amplitude by more than half [1]. Wong and Fieger subsequently suggested, using 20 mM capsazepine intradermally, that transient receptor potential vanilloid type-1 (TRPV1) inhibition blunts the initial peak to a similar extent [2]. The authors suggest that TRPV1 channels may be directly activated by heat, thereby depolarizing afferent sensory nerves to initiate the initial 'axon reflex' [2,3]. This is the hypothesis we schematized in our figure. However, Professor Szolcsanyi reminds us of the lack of involvement of axonal conduction in the release of calcitonin gene-related peptide (CGRP) or substance P evoked by the TRPV1 agonist capsaicin, because it is not inhibited by local anesthetics. Taking this evidence together, the overlap between a TRPV1-dependent pathway and another sensory nerve pathway inhibited by local anesthetics is unknown. If they are distinct, interactions between these pathways are possible, especially considering the complex effects of lidocaine on TRPV1 activation and sensitization [4]. Moreover, downstream mediators responsible for cutaneous vasodilation (CGRP, substance P or another mediator, which we represented on our figure as putatively being involved) have not been identified yet. Clinical studies simultaneously exploring the effect of sensory nerve blockade and TRPV1 inhibition during local thermal hyperemia in the human skin would therefore be of great interest.

Other issues should be stressed. The tools used in the different studies have limitations. Until recently, capsazepine was used as a specific TRPV1 antagonist. However, the relatively low affinity of this compound, together with its nonspecific inhibition of smooth muscle contractility, makes differentiation between specific and nonspecific effects difficult [5]. Capsazepine, for a long time the only TRPV1 receptor antagonist, is no longer recommended for this purpose, and we therefore question the specificity of 20 mM capsazepine used in the study by Wong and Fieger. By contrast, application of lidocaine to healthy skin induces differential effects on different sensory modalities [4].

Another point is the wide distribution of transient receptor potential (TRP) channels. Whereas most of the literature focuses on TRP expressed in the nervous system and implicated in pain signaling through sensory nerve activation, TRPV1 is also expressed on human endothelial and smooth muscle cells [6]. Apart from the neurogenic response, TRPV1 expressed on smooth muscle cells causes direct vasoconstriction, whereas TRPV1 expressed on endothelial cells causes endothelial-derived relaxation. Indeed, whereas capsaicin evokes skin vasodilation through sensory nerve activation at low concentrations, higher concentrations induce vasoconstriction due to non-neuronal TRPV1 stimulation [7]. Wong and Fieger also showed that the plateau phase of local thermal hyperemia (i.e., the 'NO component' of the response, unaffected by local anesthesia [1]) is reduced when TRPV1 channels are inhibited by capsazepine [2]. This supports the hypothesis that TRPV1 expressed in the human skin vasculature may modulate vascular tone independently from sensory nerves, which we tried to schematize in our figure.

The last issue is that although most hypotheses focus on TRPV1, laser Doppler experiments mostly use local heating at 42–43°C, below the level of noxious heating. Therefore, this temperature range will mostly activate capsaicin-insensitive TRPV3 and TRPV4, whereas TRPV1 starts to conduct a significant inward cation current when the temperature rises above 43°C [8,9]. Interestingly, the main sites of TRPV3 and TRPV4 expression on the skin tissue are not sensory nerve endings, but keratinocytes, which also express TRPV1 [10]. Therefore, mild warm stimuli to the skin may be detected initially in keratinocytes and then excitation is transferred to sensory neurons via an extracellular mediator, which has been suggested to be ATP or PGE2, conveying thermal information to sensory neurons [11]. One unifying hypothesis to be tested is that mild local skin heating activates keratinocyte TRPV3 and TRPV4, which in turn release an extracellular mediator acting on sensory nerve endings, vascular smooth muscle, and endothelium.

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e-Phytovigilance for misleading herbal information

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We read with interest the paper 'Pharmacovigilance and use of online health information' by Masoni *et al.* and we would like to congratulate the authors for highlighting the use of online health information and its relevance for pharmacovigilance [1]. We would also like to add some important information about the role of the Internet in herbal pharmacovigilance (e-Phytovigilance).

The use of complementary and alternative medicine (CAM) is steadily increasing. A recent systematic review revealed that the average prevalence of CAM use by physicians in the UK was 20.6% (range 12.1–32%) [2]. Unfortunately, consumers and healthcare-givers often ignore important problems such as herbal–drug interference and side effects, or simply the uselessness of various herbal extracts sometimes taken for many years to prevent diseases and long-term toxicity, believing that 'natural' is synonymous with 'safe' [3]. Because the use of natural health products is poorly regulated, many herbal products on the market have not been thoroughly tested for their pharmacology and toxicology, especially in pregnancy or lactation. Moreover, toxicity of herbal products arising from poor quality, incorrect or misidentified herbs, incorrect processing methods, or the supply of adulterated or contaminated herbs is also a serious problem [4].

The Internet now plays an important role in the spread of pseudo-scientific information, often mixed with serious scientific information, a problem further exacerbated by the easy availability of products through online sales. Unfortunately, there has been an increase in the number of websites that publish and disseminate incorrect information about natural products, and even recommend them in some cases, a use that can actually be proven harmful to health. The lack of regulation of information published on the Internet means that some 'alternative therapies' are being promoted without full appreciation of their potential toxicity.

Online information often presents therapeutic indications that can actually harm patients [5], for example, by promoting worrying medical claims or including the use of toxic products. In a recent survey, 522 Italian web sites containing information about the use of germander (*Teucrium chamaedrys*) were screened and only 63% of them reported correct information on the toxicity of this herb, which can easily be purchased online [6]. This example is striking given that *T. chamaedrys* L. has become popular as a slimming decoction without any scientific proof of efficacy and notwithstanding its well-known hepatotoxicity [7], and its use is even banned by health authorities.

Therefore, because the Internet is not well regulated, it is up to members of the medical community to be vigilant. Unfortunately, the simple measure of asking about the use of herbal extracts when taking a patient's history is still far from a regular practice. Masoni *et al.* highlighted important suggestions to Google regarding searches for medical information [8]. The authors proposed that Google should improve its filters so that sponsored links are not displayed for search results for medical terms or products. To support their conclusion, they searched for the term *Aloe arborescens*. The search results returned pages full of statements indicating how *A. arborescens* can cure many types of cancer, which is indeed a case indicating the need for e-Phytovigilance.

Against this background, the inclusion of natural products in pharmacovigilance systems should be mandatory. In Italy, as well as in most other countries, the National Pharmacovigilance System (directed by the Italian Medicines Agency, AIFA) collects spontaneous reports only for registered drugs, but awareness of the need for safety surveillance of natural health products has led to implementation of a reporting system for suspected adverse reactions specifically for natural products [9]. It is clear that for both pharmacovigilance and phytovigilance, adverse drug reaction (ADR) forms should be further improved, in particular to include Internet information as suggested by Masoni *et al.* [1]. Furthermore, it would be desirable to set up a task force of online medical observers who could provide correct information on herbal products

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