Brassicaceae as source of H2S-releasers: Tuscan black kale for pain relief

1) L. Di Cesare Mannelli 2)E. Lucarini 3)L. Micheli 4)M. Maresca 5)B. Tenci 6)E. Trallori 7)K. Awada 8)R. Iori 9)L. Testai 10)A. Martelli 11)V. Calderone 12)C. Ghelardini

University of Florence

Glucosinolates (GLs) are responsible for most of the beneficial effects of Brassicaceae family plants. Among them, one of the most studied is glucoraphanin (GRA), found notably in Tuscan black kale (TBK, Brassica oleracea L. var. acephala sabellica). GRA, by the enzymatic action of myrosinase, releases the isothiocyanate sulforaphane (SFN). The efficacy of these phytochemicals in models of neurological diseases, as well as their safety, have been shown. Recently, the release of hydrogen sulphide (H2S) has been related to many pharmacological properties of isothiocyanates-based compounds. The gasotransmitter can modulates the activity of Kv7, a class of voltage-gated potassium channels which plays a pivotal role in pain modulation. The aim of the present study was to evaluate the effectiveness of a TBK-sprouts extract enriched in GRA (14%) in reducing neuropathic pain induced by chemotherapeutic drugs. Pain relieving effects of GRA and SFN were studied to individuate their role in the pharmacodynamic of the extract. With this purpose the importance of H2S releasing ability and the potential involvement of Kv7 potassium channels in pain modulation of these compounds were investigated. Mice were treated daily with oxaliplatin (2.4 mg kg-1 i.p.) to induce neuropathic pain and acute behavioral tests were performed on day 15. A single subcutaneous administrations of GRA (4.43-119.79 µmol kg-1) or SFN (1.33-13.31 µmol kg-1) as well as TBK-sprouts extract (equimolar dosage of GRA) reduced the hypersensitivity to cold non-noxious stimuli (allodynia-related measurement) in a dose-dependent manner. The H2S-binding molecule Hb abolished the pain-relieving effects of GRA and SFN. The anti-neuropathic properties of both molecules were reverted by the Kv7 potassium channel blocker XE991. Moreover, to evaluate possible preventive effects, GRA and SFN were administered in a different group once daily p.o. and s.c. starting from the first day of oxaliplatin injection until the 14th and behavioural test were performed on days 7 and 14. Repeated GRA (13.31 µmol kg-1) and SFN (4.43 µmol kg-1) administration completely prevented the chemotherapy-induced hypersensitivity to thermal stimuli back to the level of healthy controls. GRA and SFN reduce neuropathic pain by releasing H2S and show a protective effect against the development of chemotherapy-induced neuropathy. The anti-hyperalgesic effect of TBK-sprouts extract is closely related to the content of the GLs. SFN is three times more potent than GRA suggesting that the glucosinolate must be metabolized to isothiocyanate before releasing H2S. The anti-hyperalgesic effect is largely mediated by the activation of Kv7 channels.