THE PROTECTIVE EFFECT OF OLIVE OIL PHENOLS HYDROXYTYROSOL AND OLEUROPEIN ON MORPHINE TOLERANCE

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Morphine and related opioid drugs are currently the major drugs for acute severe pain. Their clinical utility is limited however in the management of severe chronic pain (for example cancer pain) due to the rapid development of tolerance to their analgesic effects. A consequence of this tolerance is the need to greatly increase the dose to sustain the analgesic effect. Restoring opioid efficacy is therefore of great clinical importance. A great body of evidence suggests the key role of N-methyl-D-aspartate (NMDA)-receptor activation in opioid tolerance. NMDA-receptor activation has also been associated with overt production of superoxide, an event that leads to hyperalgesia and glutamate-induced neurotoxicity. The associations of many glutamate actions with the formation of superoxide led us to hypothesize that superoxide is an important mediator of morphine tolerance. Epidemiological studies have shown a relationship between the Mediterranean diet and a reduced incidence of pathologies such as coronary heart disease and cancer. A central hallmark of this diet is the high consumption of virgin olive oil as the main source of fat wich conteins antioxdant components in the nonsaponifiable fraction, including phenolic compuonds absent in seed oils. Here we show that in a rodent model of opiate tolerance, that removal of the free radicals with phenolic compuonds of olive oil such as hydroxytyrosol and oleuropein re-instates the analgesic action of morphine. Chronic injection of morphine in mice led to the development of tolerance and this was associated with increased oxidation of hydroethidine (HE) and malonildialdeide (MDA) formation in the spinal cord as evaluated by HPLC measurement and immunohystochemistry. Removal of free radicals by hydroxytyrosol and oleuropein blocked morphine tolerance together with HE oxidation and MDA formation. In this study we demonstrate that the phenolic fraction of virgin olive oil exerts antioxidant activities in vivo and that free radicals generation occurring during chronic morphine administration play a crucial role in the development of opioid tolerance. Our data suggest novel therapeutic approach in the management of chronic pain, in particular for those patients who require long-term opioid treatment for pain relief without development of tolerance.