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THE ENDOCANNABINOID PALMITOYLETHANOLAMIDE IS THERAPEUTICALLY EFFECTIVE IN RAT ACUTE INFLAMMATION

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The endocannabinoid palmitoylethanolamide behaves as an autacoid able to modulate the mast-cell response to inflammation and so it may represent a new anti-inflammatory agent. Moreover, it has been reported that palmitoylethanolamide was effective in reducing carrageenan, formalin and dextran-induced edema in rats, in a time and dose dependent manner.
To date, palmitoylethanolamide anti-inflammatory efficacy was assessed only when the drug was administered before the inflammatory stimulus and nothing is known about the curative effect of this drug at initiated inflammation. Thus, the first aim of the present work was to investigate whether palmitoylethanolamide was able to reduce the edema when therapeutically administered in a rat model of acute inflammation induced by carrageenan injection. This acute inflammation is characterized by vasodilatation, plasma extravasation and polymorphonuclear neutrophil influx and its development depends on various mediators including histamine, 5-hydroxytryptamine (5-HT), bradykinin, prostaglandins (PG), nitric oxide (NO) and other free radicals. On these basis, it has been interesting to verify if repeated administration of palmitoylethanolamide influenced cyclooxygenase (COX) activity, PGE_2, NO and other free radicals production, measured *ex vivo* at the site of inflammation. This study has been carried out in comparison with the classical non steroidal anti-inflammatory drug indomethacin.
Acute inflammation was induced in the rat by intraplantar injection of 0.1 ml carrageenan (1%). Palmitoylethanolamide (1, 3, 5, 10 mg/kg) and indomethacin (5 mg/kg) or the vehicle (carboximethylcellulose 1.5%) were orally administered the first day 2 h after carrageenan and the second and third day at the same time of the first injection. The paw volume was measured with a plethysmometer every day for 4 days. Subsequent daily administration of palmitoylethanolamide, as well as indomethacin, resulted in a time-dependent decrease of edema and on the fourth day palmitoylethanolamide (1,3,5 and 10 mg/kg) decreased edema in a dose-related fashion, in particular palmitoylethanolamide (10 mg/kg) abolished the inflammation, bringing the paw volume down to that found in non inflamed animals. The fourth day, after recording edema, animals were sacrificed and COX activity and content of PGE_2, nitrite/nitrate, malondialdehyde, endothelial and inducible nitric oxide synthase (eNOS and iNOS) were evaluated in the paw tissues. All these biochemical parameters resulted markedly increased in animals inflamed with carrageenan, except iNOS which disappeared at this time. Repeated treatment with palmitoylethanolamide (10 mg/kg) and indomethacin brought COX activity and the levels of PGE2, nitrite/nitrate, malondialdehyde and eNOS down to the value detected in non inflamed paw tissues.
Our findings extend previous observations of palmitoylethanolamide anti-inflammatory activity showing its curative efficacy in a rat model of acute inflammation induced by carrageenan, and indicate that palmitoylethanolamide anti-inflammatory action could be linked to its ability to affect various mediators involved in inflammation.