UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title
Pharmacological approaches targeting neuroinflammation to improve opioid safety and analgesic efficacy
2)Abstract (max 500 words)
Chronic pain represents a major global health burden, affecting approximately 20% of the world's population. Opioids are the most widely used class of analgesics for the treatment of acute and chronic pain. However, their chronic use is limited by the development of analgesic tolerance, opioid-induced hyperalgesia, and risk of abuse. Increasing evidence indicates that opioids can activate the innate immune cascade in the CNS, promoting the production of pro-inflammatory factors and resulting in neuroinflammation. These events are closely associated with reduced analgesic efficacy and exacerbation of opioid side effects. Glial cells, including microglia and astrocytes, are the key cellular mediators of neuroinflammatory responses in the CNS. Their protracted activation promotes persistent neuroinflammation that ultimately impacts neuronal transmission and plasticity. This project aims to investigate whether pharmacological modulation of neuroinflammatory pathways can mitigate opioid-induced adverse effects and potentially enhance analgesic efficacy. To address this, *in vitro* studies will employ primary rodent microglial and astrocyte cultures, as well as human iPSC-derived models, to characterize opioid-induced inflammatory responses, including cytokine release and intracellular signaling pathways, using immunocytochemistry, enzyme-linked immunosorbent assays, and gene expression profiling. Candidate pharmacological strategies targeting neuroinflammatory signaling will be identified and evaluated, and their efficacy subsequently validated in preclinical *in vivo* models by assessing behavioral outcomes (*e.g*., analgesia, hyperalgesia, and tolerance), together with molecular markers of CNS inflammation. By combining *in vitro* and *in vivo* approaches, the project will investigate not only the effects of opioids on neuroinflammatory signaling but also the mechanistic interplay between opioid receptor activation, glial responses, and downstream inflammatory cascades. The outcomes of this project are expected to provide insights into safer opioid therapies and advance our understanding of the interplay between pain management, neuroinflammation, and drug safety. During the PhD program, the candidate will acquire expertise in *in vitro* and *in vivo* neuropharmacological models and behavioral and molecular assays, gaining the skills necessary for designing, executing, and interpreting preclinical research in CNS drug development.