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EDITORIAL

From childhood to adulthood: serotonin as a link between early experiences and persistent pain

Da infância à vida adulta: a serotonina como elo entre experiências iniciais e dor persistente

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Chronic pain remains one of the greatest challenges in contemporary medicine, affecting around 20% of the world's adult population. Its impacts go beyond individual suffering, imposing functional limitations and significant socioeconomic costs. Despite advances in pharmacology and neuroscience, prevention and effective management still represent a critical gap.

Emerging evidence suggests that the early year of age plays a central role in vulnerability to chronic pain. Early painful experiences and alterations in the serotonergic system can remodel pain modulation circuits, favoring central sensitization and increasing the risk of pain syndromes in the future. Preclinical models and clinical data show that neonatal insults, from invasive procedures in intensive care units (ICUs) to psychosocial issues, can program risk or resilience trajectories, with lasting repercussions on mood, sleep and stress response[1].

Serotonin, a key neurotransmitter for pain modulation, exerts complex and bidirectional effects. Disturbances during critical periods of development can reduce descending inhibition, alter the balance between receptors and compromise synaptic plasticity, creating a pro-nociceptive scenario. Early pharmacological or environmental interventions demonstrate that it is possible to modulate this risk, but also warn of paradoxical effects of certain drugs, such as selective serotonin reuptake inhibitors (SSRIs), during development.

The concept of developmental programming, according to which early experiences shape health trajectories throughout life, is well-established in areas such as endocrinology and psychiatry. In the pain research field, this perspective is becoming more and more important. Studies in rodents show that neonatal insults, such as repeated needle punctures (pinprick), carrageenan-induced inflammation or maternal separation, result in persistent hyperalgesia and an enhanced response to painful stimuli later in adulthood[2-4].

The serotonergic system plays a central role in this process: neurons in the dorsal raphe nucleus project to multiple cortical, subcortical and spinal regions, modulating nociception in an inhibitory or facilitating way, depending on the receptor subtype[5]. Alterations in this system during the critical development period reduce descending inhibition and unbalance signaling via 5-HT1A/1B and 5-HT2/3 receptors, promoting central hyperexcitability and higher sensitivity to pain.

Preclinical studies show that fluoxetine, an selective serotonin reuptake inhibitor (SSRI), may have paradoxical effects: when administered at critical stages of development, it increases thermal and mechanical hypersensitivity in some models, but also normalizes prenatal stress-induced hyperalgesia in others[6,7]. These findings reflect the complexity of serotonin pharmacology: the final effect depends on age, the context of stress and the predominant receptor subtype, highlighting the need for caution in the neonatal prescription of SSRIs.

Furthermore, interventions that reduce serotonin, such as depletion by pCPA or 5,7-DHT, show that low levels of this neurotransmitter compromise the inhibitory modulation of pain, increase inflammatory hyperalgesia and reduce efficacy of opioid analgesics[8,9]. The interaction between serotonin, the HPA axis and synaptic plasticity suggests an integrative mechanism by which early adversity programs vulnerability to chronic pain.

These findings suggest that health policies and practices could benefit from including early preventive strategies, such as optimizing neonatal analgesia, reducing unnecessary painful procedures, strengthening parental care and carefully monitoring the use of serotonergic drugs. Using biomarkers and targeted interventions could make it possible to identify children who are at most risk and act before pain becomes chronic.

To understand the role of serotonin and early experiences in chronic pain goes beyond basic science, creating a public health dilemma and guiding the need for care policies from the first days of life. By acting early, we can not only treat, but prevent chronic pain, reducing its global impact and promoting a healthier and more resilient society.

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