

Peer Review

Review of: "The Multifaceted Nature of Pain in Sickle Cell Disease: From Molecular Mechanisms to Emerging Therapeutic Frontiers"

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This review article on pain and pain mechanisms in SCD is a comprehensive and well-written article that not only describes underlying mechanisms but also includes basic mechanisms of pain transmission and new approaches to treat sickle pain. This review article includes a wide array and appropriate list of references. The figures and tables are clear and informative. This article provides an excellent overview of pain in SCD, underlying mechanisms, and potential new treatments. There are only some minor suggestions for improvement.

1. Peripheral sensitization (nociceptor sensitization) should be clearly defined (decrease in response threshold, increased action potential discharge to suprathreshold stimuli, and spontaneous activity).
2. Central sensitization plays a major role in various pain states, particularly allodynia. Central sensitization should also be clearly defined with underlying mechanisms that include changes in descending modulatory pathways (ON and OFF cell activity in the RVM) as well as changes in the spinal cord. Understanding the changes that occur at various levels of the pain pathways may provide new targets for treatment.
3. Using a new model of cold-evoked vaso-occlusive pain in mouse studies, it was recently shown that a beverage carbonated with N₂O might be a possible new treatment for acute VOC pain (see Oddo et al.). It was also recently shown that lysophosphatidic acid contributes to chronic pain in SCD and that blocking receptors for LPA might be an effective approach for treating chronic pain (see Viatchenko-Karpinski et al.)

Declarations

Potential competing interests: No potential competing interests to declare.