Research confirms that melatonin could prevent sepsis, top cause of death in hospital ICUs

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The research team from the UGR

Sepsis is a serious disease that takes place when the body has an excessive immune response to a bacterial infection. It's the leading cause of death in hospitaL intensive care units (ICUs), and there's no specific treatment for at present. Although it is a systemic inflammation, known anti-inflammatories are not effective.

Now, researchers from the University of Granada (UGR) belonging to the Centro de Investigación Biomédica (Centre for Biomedical Research) have discovered that melatonin, a naturally occurring hormone also used as a medication, could be of use for preventing sepsis.

The results of their work have been published in the *FASEB Journal*, and were shown in July in the FASEB Science Research Conference "Melatonin Biology: Actions and Therapeutics," which took place in Lisbon (Portugal).

This research has confirmed that NLRP3 inflammasome activation "is required and necessary" in the systemic inflammatory response and is extremely serious in sepsis. Additionally, the UGR researchers have discovered the molecular targets for melatonin that back its high efficacy as an anti-inflammatory, a property that is being assessed in clinical essays in laboratory.

The NLRP3 inflammasome is ultimately responsible for the maturation of pro-inflammatory cytokines (proteins regulating cell function) which, as in the case of pro-IL-18 and pro-IL-33, are induced in an inactive way by NF-kB, the classic path of innate immunity.

The study carried out by lead author José Antonio García Santos identified the link between the classic way of innate immunity (NF-kB) and the complementary one (NLRP3).

The NLRP3 inflammasome role

"We've been able to confirm that the NLRP3 inflammasome activation is required and necessary in the systemic inflammatory response in sepsis, given that it's ultimately responsible for the maturation of pro-inflammatory cytokines which, as is the case of pro-IL-18 and pro-IL-33, are induced in an inactive way by NF-kB."

Being activated by NLRP3 inflammasome, this cytokines, specially IL-1beta, positively feed back NF-kB, thus amplifying the immune response, which determines the overwhelming immune response of the systemic inflammation in sepsis.

The researchers then studied the mechanisms responsible for inflammasome activation in mice. Thanks to ROR-alfa, a nuclear receptor for melatonin, in the inhibition of innate immunity, they

idenfified this receptor as the mechanism of melatonin's anti-inflammatory action, which also stimulates the mitochondrial bioenergetics and inhibits the NLRP3 inflammasome, thus slowing down the production of free radicals.

"With this research, we have confirmed the bases for chronic inflammation as an essential mechanism promoting the link between NF-kB/NLRP3 and systemic inflammation in sepsis. The disruption of this link, caused by melatonin, inhibits all innate immune ways activated in sepsis, which lets the body to recover from the septic shock and multiple organ failure, and significantly increases survival," professor García Santos says.

More information: J. A. Garcia et al. Disruption of the NF- B/NLRP3 connection by melatonin requires retinoid-related orphan receptor- and blocks the septic response in mice, *The FASEB Journal* (2015). DOI: 10.1096/fj.15-273656