PRO-INFLAMMATORY CYTOKINES, IL-1β AND TNF-α, PRODUCE PERSISTENT COMPROMISE IN TONIC IMMOBILITY DEFENSIVE BEHAVIOR IN ENDOTOXEMIC GUINEA PIGS

Aline Barbosa Ribeiro[1], Procópio Cléber Gama de Barcellos-Filho[1], Celso Rodrigues Franci[1], Leda Menescal-de-Oliveira[1] and Rafael Simone Saia[1]

[1] Department of Physiology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

Sepsis has been associated with acute behavioral changes in humans and rodents, consisting a motivational state and an adaptive response that improve survival. The initial phase of sepsis is characterized by the overproduction of cytokines that are essential components in the bidirectional communication between the peripheral immune system and the central nervous system. Furthermore, they are also related to affective and cognitive impairments. The tonic immobility (TI) is an ancient behavioral response with elevated adaptive significance. However, the involvement of peripheral cytokines synthesized during systemic inflammation as modulators of the TI defensive behavior remains a literature gap. Our aims were to characterize the TI defensive behavior in endotoxemic guinea pigs at acute phase and after recovery from the initial immune challenge. Furthermore, we investigated whether periaqueductal gray matter (PAG) exists as a brain structure related to this behavior and also pro-inflammatory cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-1β, act at this mesencephalic nucleus. Our results showed that endotoxemic guinea pigs exhibited a reduction in the duration of TI episodes, starting at 2h after LPS administration and persisting throughout the experimental period evaluated over 7 days. Moreover, endotoxemia increased the c-FOS immunoreactivity of neurons in the ventrolateral PAG (vlPAG), as well as the caspase-3 expression. The LPS microinjection into vlPAG reproduces the same compromise, i.e. a decrease in the duration of TI defensive behavior, observed after the peripheral administration. The immunoneutralization against IL-1β and TNF-α into vlPAG reverts all the effects produced by peripheral LPS administration. Our findings confirm that vlPAG is an important brain structure involved in the behavioral alterations induced by endotoxemia, possibly changing the neuronal activity caused by pro-inflammatory cytokines produced peripherally.