ABSTRACT (ENGLISH)

Sepsis associated encephalopathy (SAE) is a severe complication of sepsis leading to high mortality and long-term brain dysfunction. SAE often manifests as altered consciousness, delirium, coma, inattention and cognitive impairments. Sleep disturbances depicted as sleep-wake fragmentation occurring in the acute phase of sepsis have been directly linked to the poor outcomes in sepsis patients. Septic shock survivors typically develop post-sepsis syndrome characterised by extreme fatigue, sleep disturbances and cognitive impairments. Central nervous system specifically hippocampus is one of the first regions that gets affected as a result of SAE. Despite the role of sleep in maintaining a functional immune system and its importance in memory consolidation, an in-depth understanding of sleep-wake patterns remains poorly understood. In the present work, we aimed at understanding the fine dynamics of the hippocampal oscillations in an lipopolysaccharide (LPS) model of sepsis (10mg/kg) under urethane anaesthesia. Urethane exerts minimum effects on respiratory and cardiovascular system making it a suitable system to study fine kinetics of brain oscillations without any external sensory modalities. Next, we aimed at confirming our findings on sleep architecture and spectral properties in unanaesthetised animals under a standardised dose of 5mg/kg LPS. Furthermore, we aimed at understanding hippocampal CA1 cellular response to sepsis. We found that LPS led to extensive state fragmentation in both, urethane injected and unanaesthetised model of sepsis. In urethane model of sepsis, we used a 2D state space approach to study the dynamics of REM-like and NREM-like states with respect to each other. LPS resulted in increased spectral similarity and velocity driven by low (1-9 Hz) and high frequency (15-45 Hz) component respectively. The parametrization of periodic and aperiodic components of REM and NREM spectra showed that the spectral changes during sepsis were more prominently driven by the oscillatory component. We found similar state fragmentation in unanaesthetised rats accompanied by REM suppression. Spectrum analysis showed LPS-associated dampened power for up to at least 25 Hz frequency during sleep sessions. Furthermore, hippocampal CA1 interneuron and pyramidal activity decreased after 1 and 4 hrs of LPS injection, respectively. Incidence of sharp wave ripples increased post LPS.

Decreased inter-state distance accompanied by increased with-in state velocity may represent a key feature in altering the oscillatory landscape of brain state attractors causing

sleep-wake fragmentation. This may further result in failure to attain deep restorative NREM sleep associated with poor sleep quality in sepsis survivors and animal models of SAE. Dampened hippocampal cellular response and increased synchrony events after LPS injection may signify altered hippocampal network processing which may play a key role in cognitive impairment in septic shock survivors.