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SPECT and MRI evaluation increases understanding pathophysiology in a murine model of sepsis associated encephalopathy

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Sepsis-associated encephalopathy (SAE) is a frequent and devastating complication of severe acute systemic inflammation that can cause both acute and long-lasting neurological dysfunction and heavily contributes to the mortality of patients with sepsis. The knowledge of the pathophysiological processes overwhelming the brain at this early stage of sepsis is far from complete. The purpose of this study was to evaluate an approach combining SPECT and anatomical MRI methods using also a set of widely used nuclear medicine imaging agents as possible methods to study the early effects of systemic inflammation on the living brain in a mouse model of sepsis associated encephalopathy (SAE). The lipopolysaccharide (LPS) induced murine systemic inflammation model was selected as a model of SAE.
A multimodal imaging protocol was carried out on each mouse 4 hours following the intravenous administration of LPS using the following tracers: [99mTc]HMPAO and [125I]iomazenil to measure brain perfusion and neuronal damage respectively; [18F]FDG to measure cerebral glucose uptake. We assessed microglia activity on another group of mice using [125I]CLINME. Radiotracer uptakes were measured in different brain regions and correlated. Microglia activity was also assessed using immunohistochemistry. Brain glutathione levels were measured to investigate oxidative stress.
The results of SPECT measurements illustrates significantly reduced [99mTc]HMPAO uptake in the LPS treated group. Following perfusion compensation process significantly enhanced [125I]iomazenil uptake values were registered in the LPS treated group's cerebellum and hippocampus. Significantly enhanced [18F]FDG uptake was registered in the treated group compared to the control. Relevant [18F]FDG uptake was seen in the treated animals'hippocampus but this difference was not significant.
Significantly enhanced [125I]CLINME uptake was registered in all of the investigated brain regions in the LPS treated group compared to the control animals. In both groups [18F]FDG and [125I]iomazenil uptake showed highly negative correlation in all brain region. No significant differences were detected in the glutathione levels between the groups. The CD45 and P2Y12 double labelling immunohistochemistry showed widespread microglia activation in the LPS treated group.

Our results suggest that inflammatory processes can directly contribute to the uptake of [125I]iomazenil and [18F]FDG masking the neuroinflammation-induced neuron damage and hypometabolism of neural tissue respectively. [99mTc]HMPAO and [125I]CLINME can be used to detect cerebral hypoperfusion and microglia activation respectively as early as 4h following the i.v. injection of LPS. The negative correlation between the measured uptake values (low [99mTc]HMPAO, high [125I]iomazenil and [18F]FDG uptake) could also indicate the severity of brain involvement during systemic inflammation: low perfusion coupled with massive immune cell activation indicated by high [125I]iomazenil and [18F]FDG uptake. Further investigation of the metabolic activity of different brain cells and the status of the GABA receptor system would be necessary to determine the exact source of the measured signal differences during the early phase of systemic inflammation.

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