

Functional isotope imaging evaluation of terutroban efficiency in a pro-inflammatory rat model of subarachnoid haemorrhage (SAH)

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BACKGROUND

- Delayed cerebral ischaemia (DCI) is the first cause of morbidity after subarachnoid haemorrhage (SAH) [1].
- F2isoprostanes and eicosanoids were found in the cerebrospinal fluid (CSF) of patients with DCI. These potent vasoconstrictors induce platelet aggregation and mediate inflammation[2] by a thromboxaneprostaglandine (TP) receptor binding.
- The aim of our study was first to estimate the occurrence of DCI in a proinflammatory state using an high omega 6 polyunsaturated fatty acid (w6) diet and secondly to evaluate the efficiency of terutroban (TER) a TP receptor inhibitor.

MATERIALS AND METHODS

- Ninety wistar rats (400g) were randomly assigned to one of 5 groups: a double 250µL intracisternal injection of autologous arterial blood (SAH groups) or artificial CSF (CSF group) was performed [3].
- To induce a proinflammatory state animals were fat with w6 during 6 weeks before SAH procedure (SAH_w6/SAH_w6+TER). TER was administered (30mg/kg/day) during 5 days following SAH (SAH+TER/SAH_w6+TER groups).
- Evaluation of uptakes of 3 [^{99m}Tc] radiolabeled agents was achieved using microSPECT/CT imaging: HMPAO at D5 for cerebral perfusion quantification; DTPA at D3 for blood brain barrier (BBB) integrity study; and AnnexinV at D4 for apoptotic activity study. ANOVA followed by Student's t test.



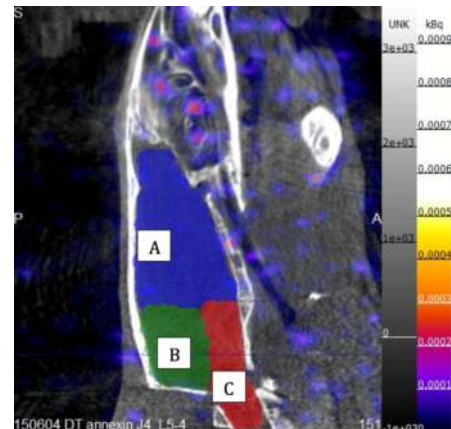
[Percutaneous puncture of the cisterna magna between the occiput and the atlas with the head held in a stereotaxic frame]



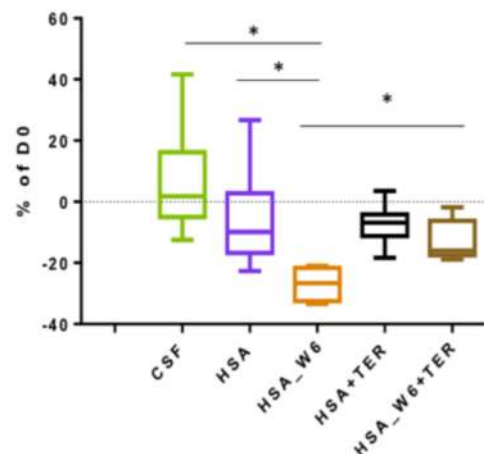
[microSPECT/CT imaging]

RESULTS AND DISCUSSION

- HMPAO uptake analysis showed a significant decrease in the SAH group (figure).
- DTPA and AnnexinV uptake were also significantly increased in the SAH group compare to the CSF group. Proinflammatory state before SAH dramatically decreased HMPAO uptake (figure); increased DTPA (0.37 ± 0.04 vs. 0.43 ± 0.01 Mbeq/mm³; $P < 0.05$) and AnnexinV (0.39 ± 0.03 vs. 0.48 ± 0.03 Mbeq/mm³; $P < 0.05$).
- TER significantly counteracted the decrease in HMPAO uptake (figure) and the increase in DTPA uptake ($P < 0.05$) and in AnnexinV uptake ($P < 0.001$) induced by SAH.



[ROIs of uptake analysis: A, Cerebral hemispheres; B, Cerebellum; C, Brainstem]



[Brainstem ^{99m}TcHMPAO uptake at D5 expressed in % of D0]

CONCLUSION

- For the first time, a proinflammatory SAH rat model of DCI has been described. microSPECT study shows that a proinflammatory diet dramatically increases apoptosis and DCI.
- TER improved hypoperfusion, BBB disruption and apoptosis. TP receptor antagonists could be promising treatments after SAH.

[1] Vergouwen et al, Stroke 2011;42,924-9;

[2] Félétou et al, J Cardiovasc Pharmacol 2010;55,317-32;

[3] Dusick et al, Surg Neurol Int 2011;2,99