# Neuroprotective Effects of Kadsurenone on Transient Focal Ischemia in Rat Brain Observed by In Vivo MRI/MRS

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## INTRODUCTION

Platelet activating factor (PAF) is a potent endogenous lipid autacoid produced by neurons, endothelial cells, polymorphonuclear leukocytes and macrophages. Recent studies have shown that PAF plays a role in causing cerebral damages in stroke, and is a contributor to postischemia microcirculatory failure, blood-brain barrier damage as well as edema formation. It was also demonstrated that PAF enhances the effects of a number of mechanisms involved in the secondary brain damage such as the production of eicosanoides, free redical, cytokines and related phagocytic leukocyte reactions. Kadsurenone is a specific PAF receptor antagonist extracted from Chinese herb Caulis Piperis Futokadsurae. To investigate whether Kadsurenone could improve cerebral metabolism and protect the brain from ischemia/reperfusion injuries, its therapeutic efficiency was evaluated in a transient focal ischemia model (suture induced middle cerebral artery occlusion (MCAO) in rat by diffusion-weighted imaging (DWI), $T_2$-weighted imaging and in vivo $^1$H-MRS.

## METHODS

Wister rats (Grade Ⅱ, 220±50 g) were anesthetized by urethane (10%, 0.01g/kg ), and underwent transient occlusion of the right middle cerebral artery for 1 hour by using the suture occlusion model. Animals were randomly divided into four groups: Group A (n=6), sham-operated; Group B (n=6), ischemia/reperfusion treated with normal saline; Group C (n=6), ischemia/reperfusion treated with Kadsurenone; Group D (n=6), ischemia/reperfusion treated with Ginkgolides. Normal saline (20 mg/kg), Kadsurenone (20 mg/kg) and Ginkgolides (20 mg/kg) were injected intraperitoneally before MCAO. The rectal temperature of the rats was controlled at 37.0±1.0 $^oC$ during ischemia/reperfusion. MR experiments were carried out on a BRUKER AVANCE console connected to a 4.7 T/31 cm magnet equipped with actively shielded gradients. A volume coil was used for transmission and a 3-cm diameter surface coil was used for reception. DWI (FOV 3×3 $cm^2$; 256×256; TR=2500 ms; TE=56 ms; b=120,000 s/$cm^2$) and $^1$H-MRS(PRESS; TR= 1 s; TE=136 ms) were carried out 1 hr after reperfusion. $T_2$-weighted imaging (FOV 3×3 $cm^2$; 256×256; TR=2500 ms; TE=25 ms) was performed 72 hrs after reperfusion.

## RESULTS AND DISCUSSION

Hyperintensive areas were seen on diffusion weighted and $T_2$-weighted images after cerebral ischemia/reperfusion in Group B, C and D, which were considered as areas of brain lesions. The mean lesion volume measured by DWI 1 hr after reperfusion was 83.5±9.7 $mm^3$ in Group B, versus 14.3±5.9 $mm^3$ in the Kadsurenone-treated group (Group C; $p < 0.01$) and 22.3±8.2 $mm^3$ in the Ginkgolides-treated group (Group D, $p < 0.01$).The infarction volume derived from $T_2$-weighted images measured 72 hrs postischemia was 67.5±36.1 $mm^3$ in Group B, versus 10.5±8.6 $mm^3$ in the Kadsurenone-treated group ($p < 0.01$) and 18.5±16.1 $mm^3$ in the Ginkgolides-treated group ($p < 0.01$). Furthermore, Kadsurenone induced a significant decrease in the cerebral lactate concentration 1 hr after reperfusion. The mean peak area ratio of lactate to creatine measured by $^1$H-MRS 1 hr after reperfusion was 1.47±0.36 in Group B ,versus 0.07±0.05 in Group C ($p < 0.01$) and 0.58±0.50 in Group D ($p < 0.01$). Kadsurenone treatment had no effect on NAA, the mean peak area ratio of NAA to creatine was 1.13±0.27 in Group B, versus 1.07±0.40 in Group C ($p > 0.05$) and 0.90±0.27 in Group D ($p > 0.05$). The results show that the treatment with intraperitoneally injected Kadsurenone prior to ischemia achieved long-lasting neuroprotective effects after cerebral ischemia/reperfusion, as measured by MRI and $^1$H-MRS. As platelet-activating factor receptor antagonists, both Kadsurenone and Ginkgolides showed remarkable neuroprotective effects. Kadsurenone, and platelet-activating factor receptor antagonists in general, may therefore represent a new approach to the treatment of cerebral ischemia/reperfusion injuries.

## REFERENCES

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2.Barker PB, Gillard JH, van Zijl PC *et al*, Acute stroke: evaluation with serial proton MR spectroscopy findings. Stroke, 1995, 26: 225-229.

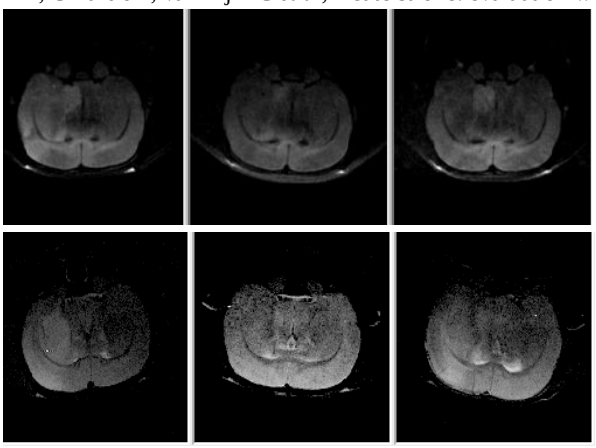

**Figure 1.** Diffusion-weighted (upper row) and $T_2$ weighted images (lower row) of rat brain measured 1 hr and 3 days after ischemia/reperfusion, respectively. Left: ischemia/reperfusion+saline group, Middle: Kadsurenone-treated group, Right: Ginkgolides-treated group.

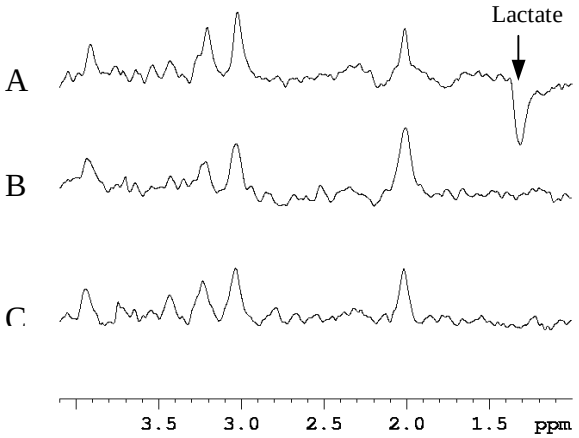


**Figure 2.** PRESS spectra (TE=135 ms) of right caudate nucleus in rat brain measured 1 hr after transient focal ischemia. (A): ischemia/reperfusion+saline group, (B): Kadsurenone-treated group, (C): Ginkgolides-treated group.