

ANTI-INFLAMMATORY EFFECTS OF PROPOFOL ON PRESSURE-STIMULATED MICROGLIAL CELLS

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Introduction: Intracranial hypertension is a frequent complication of severe traumatic brain injury (TBI), and is associated with worse clinical outcomes. TBI induces a neuroinflammatory response characterized by activation of microglia and the acute upregulation of proinflammatory cytokines. To elucidate the potential effect of elevated intracranial pressure on microglial function, we studied the effects of increased extracellular pressure on primary human microglial cell phagocytosis, proliferation and cytokine secretion. We further evaluated the effects of propofol treatment on the with observed effects.

Methods: Primary human microglial cells were maintained in DMEM Ham's F12 medium. Microglial cells were pre-treated with propofol (10 μ g/ml) or with an equivalent amount of intralipid as a vehicle control. Pressure was controlled at 30 mmHg above ambient using a prewarmed air-tight ucite box with an inlet valve for gas application and an outlet valve connected to a manometer, and control cells were maintained in the same incubator simultaneously without exposure to increased pressure. Phagocytosis was determined by the percentage of fluorescent labeled latex beads within cells under a fluorescence microscope. Cell proliferation was assessed by a colorimetric assay using crystal violet. TNF α , IL1 β and IL6 was assayed by sandwich ELISA and total nitrate by Greiss reagent.

Results: Pressure significantly increased cells phagocytosis ($37.4 \pm 2.9\%$ vs $20.0 \pm 5.1\%$, $n=3$, $p<0.01$) and proliferation ($100 \pm 3.0\%$ vs 129 ± 2.8) in microglial cells treated with the intralipid vehicle control as well as untreated cells. However, propofol inhibited pressure induced phagocytosis (36.6 ± 1.2 vs $21.8 \pm 2.6 \%$, $n=3$, $p<0.01$) but not proliferation. [figure1,2] Pressure also significantly increased microglia TNF α production (12.0 ± 0.7 vs 6.3 ± 3.5 pg/ml, $n=4$, $p<0.05$) and pretreatment with propofol inhibited the pressure stimulated effect. (4.8 ± 1.1 vs 12.0 ± 0.7 pg/ml, $n=4$, $p<0.01$). Pressure or propofol has no effect on the microglial IL-1 β or IL-6 production.[figure3] Propofol preetreatment decreased total nitrate production in microglia subjected to extracellular pressure.

Conclusion: Extracellular pressures consistent with increased intracranial pressure after head injury activate inflammatory signals in microglial cells, stimulating phagocytosis, proliferation, and TNF- α secretion. Such inflammatory events may contribute to the worsened prognosis of traumatic brain injury after increased intracranial pressure. Since propofol alleviated these potentially pro-inflammatory effects, these results raise the possibility that the inflammatory cascade activated by intracranial pressure may be targeted by propofol in patients with increased intracranial pressure after TBI.

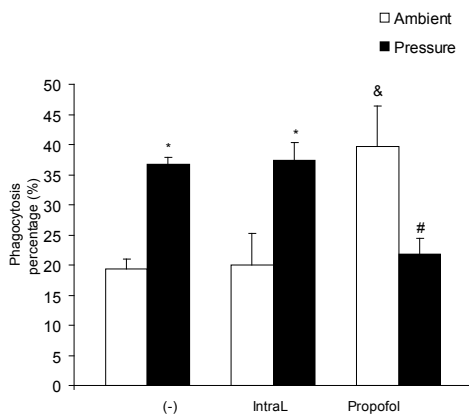


Figure 1: Effect of in vitro propofol treatment on microglia phagocytosis under ambient and increased pressure conditions. Pressure (* $p<0.01$, $n=3$) significantly increased phagocytosis in intralipid treatment or without any treatment group. Pretreatment with propofol (& $p<0.01$, $n=3$) significantly increased phagocytosis in microglial cells compared to cells treated with intralipid at ambient pressure. Propofol inhibited pressure-stimulated phagocytosis in propofol-treated cells (# $p<0.01$, $n=3$).

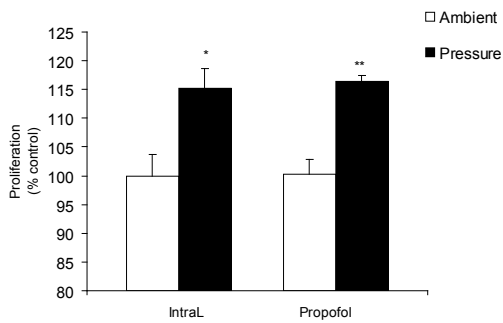


Figure 2: Effect of in vitro propofol treatment on microglia proliferation under ambient and increased pressure conditions. Microglial cells were pre-treated with intralipid (vehicle control) or propofol for 30 minutes then subjected to ambient or 30mmHg extracellular pressure. Pressure significantly increased proliferation in the intralipid group (* $p < 0.05$, $n = 3$) and the propofol pretreatment group (** $p < 0.01$, $n = 3$).

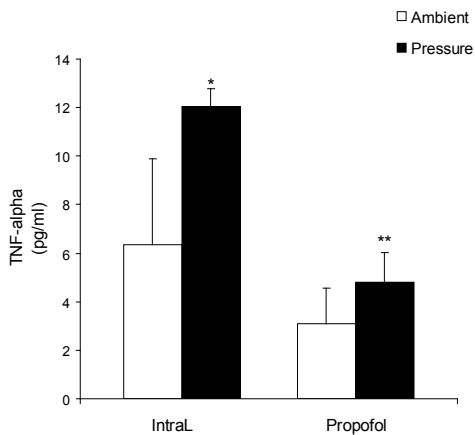


Figure 3: Effect of in vitro propofol treatment on microglia TNF α , IL-1 β and IL-6 production under ambient and increased pressure conditions. In vehicle control group pressure (* $p < 0.05$, $n = 4$) significantly increased TNF α production. Propofol inhibited pressure-stimulated TNF α production in propofol-treated cells (** $p < 0.01$, $n = 4$).

