Effects of Serotonin Signaling and Blood Pressure Modulation on Cerebral Blood Flow in Experimental Cerebral Malaria

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Introduction. Experimental cerebral malaria (ECM) is associated with cerebral vascular dysfunction and reduced cerebral blood flow (CBF). Ex vivo data, using isolated arteries, suggest that plasma from ECM animals contains serotonin (5-HT) as a strong vasoconstrictor, whose effects are enhanced under conditions of increased vascular permeability and extravasation to the abluminal environment. Based on this, we hypothesized that 5-HT contributes to vascular dysfunction and CBF reduction during ECM. **Objectives.** To characterize changes in CBF during ECM infection and to assess the effects of 5-HT receptor blockade with ketanserin and systemic blood pressure modulation in ECM. **Methods.** Mice infected with *P. berghei* ANKA underwent chronic cranial window implantation after scalp removal and application of an acrylic layer. CBF was measured at day 0 and day 6 post-infection (dpi) using laser speckle imaging. Ketanserin (5-HT_{2a} receptor antagonist, 1 mg/kg) was administered from day 3 to day 6 dpi. In separate experiments, norepinephrine (NE, 3 µg/kg/min) was infused via osmotic pumps to modulate systemic blood pressure, measured by tail plethysmography, in the presence or absence of ketanserin. **Results.** ECM was associated with a marked reduction in CBF on day 6 dpi. No differences in CBF were observed between groups at 1 or 6 hours after treatment. Ketanserin did not worsen hypotension compared with vehicle in ECM mice. NE-induced increase in systemic blood pressure failed to improve CBF. Changes in CBF were not correlated with systolic pressure. Combined ketanserin and NE treatment showed a trend toward attenuated CBF reduction at 6 hours. **Conclusion.** CBF impairment in ECM is not reversed by 5-HT receptor blockade or systemic blood pressure modulation alone. However, pressure control in the presence of ketanserin tended to limit CBF decline, supporting a contributory role of 5-HT in ECM-associated cerebral hypoperfusion driven mainly by local cerebrovascular dysfunction.