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Inflow versus outflow ischemia: differentiation and pharmacological characterization using cellular models

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Abstract:
Ischemia is a hallmark of stroke, myocardial infarction, and many other tissue injuries, and perhaps one of the best modeled human disease in laboratory animals. Nevertheless, it remains difficult to dissect the two main components of ischemia, the disruption of blood inflow versus blood outflow, in animal models. In this study, we attempt to differentiate these two components of tissue ischemia using cellular models. Inflow-ischemia is induced by exchanging the nutrient-enriched culture medium with a nutrient-less extracellular solution, thereby mimicking the loss of nutritious blood supply. Outflow-ischemia is induced by reducing the volume of the culture medium to allow more efficient accumulation of secretory products including metabolic wastes, thus resembling the disruption of blood outflow during tissue ischemia. Interestingly, while human embryonic kidney (HEK) cells are resistant to inflow-ischemia, they degenerate abruptly upon outflow-ischemia. In marked contrast, rat primary cortical neurons are highly susceptible to inflow-ischemia, but strongly resistant to outflow-ischemia. Lastly, the mouse endothelioma cells are resistant to either inflow- and outflow-ischemia alone, and degenerated only when simultaneously subjected to both components of ischemia. As proof-of-concept, we demonstrated that outflow-ischemia is transferrable between cell cultures by exchanging their culture media, and is fully reversible by re-administration of fresh culture medium. Consistent with metabolic acidosis, cell death could be exacerbated and mitigated by decreasing and increasing pH of the culture medium, respectively. Moreover, the inhibitor amiloride prevented outflow-ischemic death in a dose-dependent manner. Taken together, the data reported here showed that different cell types are differentially susceptible to different components of ischemia, and further identified amiloride-sensitive receptors as pharmacological targets against outflow-ischemia.
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