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The role of Adrenomedullin signalling in suppression of blood brain barrier permeability: a fishy perspective

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Short summary

The blood-brain barrier (BBB) is a highly selective semi-permeable interface of endothelial cells (ECs) which prevents most solutes in the blood from non-selectively crossing into the central nervous system (CNS). Transport between the circulation and the CNS is limited by the BBB via paracellular and transcellular mechanisms, but how these mechanisms are established during development remains poorly understood. We have identified a genetic program in zebrafish endothelial cells (ECs) which limits transcytosis in the BBB via the Calcrl/Ramp2 G-Protein Coupled Receptor (GPCR) complex, also known as the Adrenomedullin receptor. This complex was discovered to promote lymphatic formation and EC junctional integrity throughout the body in mice and is highly conserved between zebrafish and humans. Genetic variants in CALCRL and RAMP2 are associated with predisposition to human diseases including stroke. We have generated novel zebrafish mutants in the Adrenomedullin (AM) receptor complex (Calcrl/Ramp2) and found using live fluorescent imaging that *ramp2a* and *calcrlb* mutant embryos display widespread oedema but normal blood and lymphatic vessel formation. Loss of *calcrlb* and *ramp2a* can be partially compensated by their paralogues *calcrla* and *ramp2b*, respectively. Adrenomedullin receptor mutants display abnormal barrier establishment from 3dpf, extravasation of fluorescently labelled plasma proteins and high molecular weight dyes, and elevated transcytosis within the vasculature of the midbrain and hindbrain from as early as 4dpf. This suggests Adrenomedullin receptor signalling may be an early pathway which establishes regional differences in barrier function within the developing cerebral vasculature.

1. 8-61. *equal contribution.