SorCS2, a receptor involved in protein trafficking, plays a key role in astrocyte-mediated neurovascular coupling (NVC) by regulating glutamatergic and calcium signaling pathways.

Scientific Context

- **SorCS2**: Previously known for its role in <u>glutamatergic neurotransmission</u>, especially in the hippocampus.
- **Neurovascular coupling (NVC)**: Critical mechanism by which neuronal activity leads to local blood flow increases, largely mediated by astrocytic endfeet.

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Methods Summary

- Models used: Sorcs2 knockout (Sorcs2-/-) vs wild-type mice.
- Ages: P8 (postnatal day 8) and 2-month-old mice.
- Techniques:
 - $\circ\,$ Immunohistochemistry (SorCS2, GFAP, AQP4, CD31...)
 - \circ In vivo laser speckle contrast imaging for NVC.
 - $\circ\,$ Calcium imaging ex vivo in acute brain slices.
 - $\circ\,$ Proteomics (bulk + surface astrocyte proteome).
 - $\circ\,$ Western blot and qPCR validation.

Key Results

- Expression Pattern:
 - $\circ\,$ SorCS2 is abundant in astrocytic endfeet in young (P8) mice, sparse in older mice.
- Functional Deficit:
- Sorcs2-/- mice have impaired NVC with reduced astrocytic calcium responses.
- Proteomic Changes:
 - $\circ~$ Upregulation of glutamate receptor mGluR3 in Sorcs2-/- astrocytes.
 - $\circ\,$ Altered AQP4 distribution: $\uparrow\,$ in total lysate but $\downarrow\,$ on the cell surface.
- **No vascular structural defects** were observed, pointing to a functional rather than anatomical deficit.

Interpretation

- SorCS2 regulates astrocytic function via two mechanisms:
 - 1. Glutamatergic signaling modulation (likely feedback via mGluR3).
 - 2. Calcium signaling pathway stability, required for effective NVC.
- The mislocalization of AQP4 suggests trafficking defects, not expression-level defects.

Relevance for Neurosurgeons

- 1. Perioperative cerebral perfusion in patients with gliomas, trauma, or stroke might be influenced by astrocyte dysfunction and NVC defects.
- 2. Targeting astrocytic pathways like SorCS2 could be a future therapeutic avenue in neurodegenerative diseases or post-surgical edema management.

This study emphasizes the importance of early astrocytic regulation in developing NVC in pediatric neurosurgery, which is potentially relevant in congenital or early-onset encephalopathies.

A Critical Assessment

- Strengths:
 - Multi-modal and cross-age analysis.
 - High technical rigor (proteomics + functional imaging).
- Limitations:
 - $\,\circ\,$ Lack of behavioral correlation.
 - Findings are mostly associative; mechanistic links (e.g., SorCS2 → mGluR3 trafficking) are implied, not directly tested

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Staehr C, Login H, Melnikova EV, Bakun M, Ziemlinska E, Kisiswa L, Ardestani SB, Nolte SS, Beck HC, Hansen LMB, Postnov D, Verkhratsky A, Malik AR, Nykjaer A, Matchkov VV. SorCS2 Is Important for Astrocytic Function in Neurovascular Signaling. Acta Physiol (Oxf). 2025 Jun;241(6):e70052. doi: 10.1111/apha.70052. PMID: 40342271.

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