A textbook assumption about the brain's most abundant receptors needs to be rewritten

The AMPA group of brain receptors have mostly been assumed to be calcium impermeable and so were not thought to contribute to the calcium-dependent mechanisms underlying learning and memory. Observations of calcium permeability in some AMPA-receptor subtypes now overturn those assumptions about these receptors' properties and their roles in neuronal communication.

This is a summary of:
Miguez-Cabello, F. *et al*. GluA2-containing AMPA receptors form a continuum of Ca^{2+}-permeable channels. *Nature* https://doi.org/10.1038/s41586-025-08736-2 (2025).

Cite this as:
Nature https://doi.org/10.1038/d41586-025-00806-9 (2025).

The problem

The neurotransmitter molecule L-glutamate (L-Glu) enables fast communication between neuronal cells in the brain. On release, it binds to a diverse group of Glu-receptor proteins in neuronal cell membranes, triggering changes in the transport of ions into the cell, resulting in neuronal excitation. Excitatory communication mediated by L-Glu is crucial for normal brain function. More specifically, the formation of memory traces in neuronal circuits is enabled by the L-Glu-triggered influx of calcium ions. Since the 1990s, however, AMPA Glu receptors (AMPARs) that contain a subunit called GluA2 have been assumed to be unable to transport calcium ions[1] because the narrowest part of their pore region has positively charged arginine residues that were assumed to repel calcium. As a result, long-lasting changes to brain circuits have been attributed mainly to the actions of another group of Glu receptors, known as NMDA receptors. This distinction established a conceptual framework that is still used to explain how L-Glu promotes information storage in the brain.

This framework seems compelling, but there are reasons why assigning such a relatively peripheral role to AMPARs might need rethinking. First, the discovery of multiple families of 'auxiliary' protein subunits that co-assemble with AMPARs and modify their functionality means that the signalling capacity of AMPARs in the brain is probably greater than originally appreciated. And second, it is difficult to reconcile the association of more than 100 mutations that affect AMPAR-encoding genes with autism and intellectual disability unless AMPARs have a substantial role in the computational and memory capacity of neurons.

The discovery

We investigated the ability of AMPARs to transport calcium ions. In a collaboration published last year, we found[2] that all AMPARs have an extracellular pocket called site-G that enables them to bind calcium ions (Fig. 1). How this pocket affects calcium-ion transport was unclear, however. Previous work had shown that AMPARs assemble with auxiliary subunits from several families[3], the most prominent being TARPs and CNIHs, which are expressed in a brain region-specific manner. AMPARs in the cerebellum at the back of the brain assemble mainly with TARPs[4], whereas AMPARs in the brain's cortex and memory-forming centre, the hippocampus, also co-assemble with CNIHs[3]. We reconstructed AMPARs so they would mimic those assembled in the brain — with TARPs alone or with CNIHs — and tested their ability to transport calcium ions.

Contrary to conventional understanding, we discovered that co-assembly with TARPs alone or together with CNIHs caused a large increase in the ability of AMPARs to transport calcium ions. Remarkably, we found that auxiliary subunits follow strict rules of assembly that depend on their placement in the AMPAR complex, the type of TARP or CNIH, and the AMPAR subunits that form the ion-transporting pore. Together, the different reconstructed variants of naturally occurring AMPARs formed a continuum in their ability to transport calcium ions that spans almost two orders of magnitude. Notably, several 'missense' mutations that affect the amino acid sequence of AMPAR subunits increase the ability of the resulting AMPARs to transport calcium ions. This finding suggests that the occurrence of autism and intellectual disability in some individuals might reflect the dysregulation of calcium-ion transport by these receptors.

The implications

For 30 years, most AMPARs have been assumed to be unable to transport calcium ions, which is a crucial intracellular signal. Our study challenges this viewpoint and proposes a broader role for AMPARs in calcium signalling in the mammalian brain. Remarkably, our findings agree with wide-ranging values of calcium-ion permeability reported in much earlier studies of AMPARs from different neuron populations and in different brain regions[1]. Our study also accounts for reports of unexpected behaviour by some AMPARs that have largely been ignored[5]. How these insights fit into our understanding of the role of AMPARs in fast neuronal communication and the neuronal plasticity events involved in learning and memory remains to be resolved.

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EXPERT OPINION

"GluA2-containing AMPA receptors, which are the predominant type in the central nervous system, have long been thought to be impermeable to calcium. This paper corrects this assumption, however, by showing that GluA2-containing AMPARs exhibit varying degrees of calcium permeability. The authors show that this feature is influenced by interactions with auxiliary proteins. This work will be of interest to researchers studying ionotropic glutamate receptors, synaptic plasticity, neuronal signalling and brain development." (CC BY 4.0)

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FIGURE

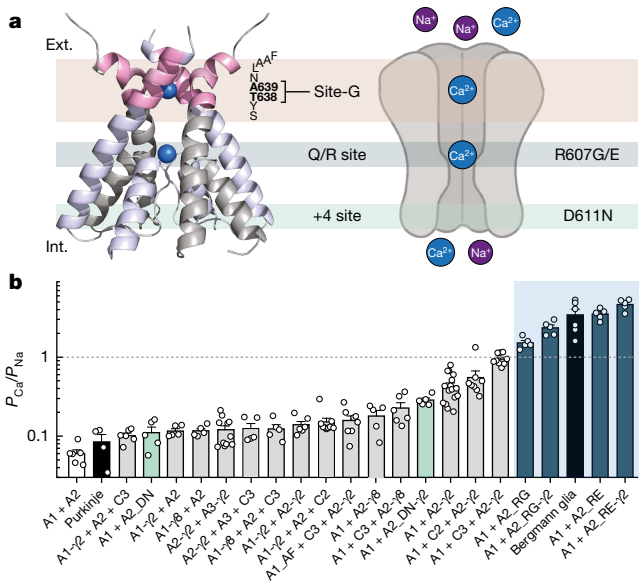

Figure 1 | AMPA receptors form a continuum of calcium-permeable ion channels. Most members of the AMPA family of receptors (AMPARs) in the brain were thought to be calcium impermeable. **a**, Pore structure and schematic of the calcium-ion transport pathway of AMPARs highlighting two calcium-ion binding sites: the Q/R site, which determines ion selectivity, and the extracellular site-G. R607G/E and D611N are missense mutations at the Q/R site and the +4 site of the pore, respectively, and are associated with autism and intellectual disability. Ext, exterior to the cell; Int, interior of the cell. **b**, AMPAR heteromeric complexes reconstructed using different subunit and auxiliary subunit combinations formed a continuum in their ability to transport calcium ions relative to sodium ions (P_{Ca}/P_{Na}). Purkinje and Bergmann glia refer to measurements of calcium permeability in these cell types. All the other receptors tested are recombinant GluA1–GluA2 or GluA2–GluA3 heteromers with TARP (γ2 and γ8) and/or CNIH (C2 and C3) auxiliary subunits. AF, GluA1 mutant. The structure in **a** was adapted from D. Zhang *et al. Nature* **594**, 454–458 (2021); the diagram in **a** was created using BioRender (https://biorender.com).

BEHIND THE PAPER

Our laboratory has known for almost two decades that many AMPARs transport calcium ions; we just didn't understand the molecular mechanism. We had a suspicion in 2007, however, when we stained neurons in the rat eye that were permeable to certain ions, including calcium ions. The stained neurons had unexpected, even paradoxical, responses to a blocker of calcium-permeable AMPARs that appeared only after eye opening (reviewed in ref. 5). We found, although never reported, that the GluA2 AMPAR subunit was a key player. This was unexpected, because GluA2 was thought to render AMPARs impermeable — not permeable — to calcium ions. The trail went cold, but later structural and proteomic studies, along with our electrophysiology work[4], revealed the strict rules of AMPAR assembly, with GluA2 having a pivotal role. The last piece in the puzzle emerged from a collaboration with structural biologist Teru Nakagawa that led to the discovery[2] of site-G and renewed our interest in calcium-ion transport.

D.B.

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FROM THE EDITOR

At its heart, this work looks to challenge a central, assumed property of receptors involved in fast excitatory neurotransmission. Causing textbooks to be rewritten is a lofty ambition for any scientific paper, but this work is likely to affect not only the scientific literature, but also a lot of current research in the field.

Bryden Le Bailly, Senior Editor, *Nature*