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Editorial

Preview: ionotropic glutamate receptor trafficking: AMPA receptors talk back

Thomas Bartlett, Yu Tian Wang

Brain Research Centre and Department of Medicine, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, British Columbia V6T 2B5, Canada

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Fast synaptic transmission at the vast majority of excitatory synapses in the mammalian CNS is mediated by the neurotransmitter glutamate. Glutamate primarily acts on two major subfamilies of postsynaptic, ionophore-linked glutamate receptors: the α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and the N-methyl-D-aspartate receptors (NMDARs). During basal excitatory synaptic transmission, glutamate binds to the extracellular domains of AMPARs and gates channel opening, mediating excitatory postsynaptic excitatory potentials (EPSPs). Normal synaptic transmission does not however involve NMDARs because these channels are subject to voltage-dependent blockade by extracellular Mg^{2+}. Conditions such as intense activation of AMPARs create sufficient depolarization to expel Mg^{2+} from the NMDAR ionophore enabling influx of both sodium and calcium ions which contribute to the EPSP. This activity-dependent activation of NMDARs in turn produces modification of AMPARs and forms the basis of the well-characterised synaptic plasticity processes Long Term Potentiation (LTP) and Long Term Depression (LTD) [1, 2]. In LTP and LTD, AMPARs are dynamically regulated by changes in trafficking and channel function to express an increase or decrease in synaptic efficacy.

Besides propagating the depolarization required for synaptic transmission and NMDAR activation, the capacity of AMPARs to change postsynaptic function directly is not well studied. Selective activation of AMPARs has been previously shown to increase AMPAR endocytosis [3], but in this issue of The International Journal of Physiology, Pathophysiology and Pharmacology (Page 47-56), Li et al report for the first time that AMPAR activation also modifies the trafficking and hence subcellular distributions of NMDARs. This raises the possibility that AMPAR activity controls not only synaptic plasticity but also metaplasticity, the changes in NMDARs that lead to subsequent changes in the properties of synaptic plasticity [4]. Additionally, the authors characterize the effect of selective activation of synaptic or extrasynaptic NMDARs on ionotropic glutamate receptor subunit surface expression, showing that synaptic and extrasynaptic NMDARs positively and negatively regulate AMPAR and NMDAR surface expression, respectively.

Following various treatments to selectively activate receptors in distinct subcellular compartments of cultured hippocampal and cortical neurons, the authors examined their impacts on cell surface expression of various subpopulations of AMPARs and NMDARs using a cell surface biotinylation protocol. Using a hypertonic sucrose solution to cause synaptic glutamate release which activates both synaptic AMPARs and NMDARs, the authors showed an increase in AMPAR GluA1 at the cell surface with no change in NMDAR GluN subunit levels. However, application of glutamate in the presence of NMDAR blockers AP5 and extracellular Mg^{2+} led to a decrease in not only GluA1 but GluN1 and GluN2A. This shows the differential effects of synaptic AMPAR and NMDAR activation on plasma membrane surface expression of iono-

tropic glutamate receptor populations. The effect of sucrose-induced glutamate release following NMDAR blockade was confirmed to be due to a selective activation of AMPARs because it was blocked by the selective antagonist GYKI 53655 and mimicked by the application of AMPA. The AMPAR-mediated process was Ca^{2+} independent as confirmed by its persistence in zero Ca^{2+} conditions, much like a previous report [3]. The hypertonic sucrose treatment in the presence of the AMPAR antagonist CNQX unmasked the effect of synaptic NMDAR activation, namely an increase in the levels of GluA1, GluN1 and GluN2A. Hence the effects of synaptic AMPAR and NMDAR activation are opposite. When the authors turned their attention to the extrasynaptic population of NMDARs, they observed a decrease in the surface population of GluA1, GluN1, GluN2A and GluN2B when extrasynaptic NMDARs were selectively activated.

This study shows that AMPAR effects on AMPAR and NMDAR trafficking are opposite to the consequences of synaptic NMDAR activation. Moreover, extrasynaptic NMDAR activation has an opposite effect on these receptors compared to synaptic NMDAR activation and only extrasynaptic NMDARs regulate the surface expression of GluN2B. These observations fit well with the functional specialization of NMDARs in different subcellular compartments, such that extrasynaptic receptors are required for LTD while synaptic receptors are required for LTP [5, 6]. It also clarifies the functional specialization of NMDAR subtypes because NR2A is predominantly synaptic in cultures while NR2B is predominantly extrasynaptic [7] and the NR2A and NR2B subtypes may specialize in LTP and LTD respectively [8].

The findings of this study highlight unappreciated roles of AMPARs in controlling the induction of synaptic plasticity, beside the well-characterized role of AMPARs in the expression of plasticity. They also reinforce the idea of specialization of NMDARs based on subcellular location. Many new questions also arise from this study, for example what is the identity of the mechanism that transduces AMPAR activation into changes in ionotropic receptor subunit surface expression? How does this AMPAR signal converge with the NMDAR signal that changes ionotropic receptor trafficking such that strong synaptic stimulation leads to the net effect of synaptic potentiation? Exactly how much are AMPA-related changes in receptor surface expression important during different forms of synaptic plasticity and do they persist for long periods? What would happen if extrasynaptic AMPARs were selectively activated?

It is now clear that the relationship between AMPARs and NMDARs is not simply one way. AMPAR surface expression is subject to autoregulation and AMPAR activation also has profound effects on the surface expression of NMDARs. This research has important consequences for information processing at the synapse and should give new impetus to efforts aimed at unraveling previously unsuspected roles of AMPAR signaling in synaptic plasticity.

Please address correspondence to: Yu Tian Wang, PhD, Brain Research Centre and Department of Medicine, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, British Columbia V6T 2B5, Canada.

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