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JAK2-STAT3 signaling

A novel function and a novel mechanism

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The function of JAK-STAT signaling in the central nervous system has been widely studied in the context of neural cell development and differentiation and in neuronal and glial responses to CNS injury. A study published recently in *Neuron* by Nicolas et al. now demonstrates that the JAK2-STAT3 pathway also plays an important role in the regulation of synaptic transmission. By using a combination of biochemical, pharmacological and genetic approaches they show that induction of long-term depression (LTD), an activity-dependent rapid and long-lasting decrease in synaptic strength, via NMDA receptors depends on STAT3 activation by JAK2 that can be localized specifically to postsynaptic structures. Most interestingly, they find that induction of LTD requires STAT3 phosphorylation and dimerization but is independent of nuclear translocation and transcriptional activity of STAT3. Although it remains to be clarified how NMDA receptor-mediated postsynaptic processes lead to JAK2-STAT3 activation and how this in turn translates into persistent changes in synaptic strength, these results provide evidence for a novel mechanism of signal transduction.

Keywords: synapse, synaptic plasticity, long-term depression, NMDA, STAT3

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Commentary to: Nicolas CS, Peineau S, Amici M, Csaba Z, Fafouri A, Javalet C, et al. The Jak/STAT pathway is involved in synaptic plasticity. Neuron 2012; 73:374–90; PMID:22284190; http://dx.doi.org/10.1016/j.neuron.2011.11.024

The paper published recently in *Neuron* by Nicolas et al.[1] is remarkable in that it provides new insights in two separate fields of research. It advances the understanding of the mechanisms underlying long-term depression (LTD), a neurophysiological phenomenon that is thought to be associated with learning and memory, by demonstrating that its expression depends on JAK2-STAT3 signaling and, particularly interesting for the reader of this journal, it provides evidence for a novel nucleus-independent JAK-STAT signaling mechanism. Long-term potentation (LTP) and LTD are the two major forms of synaptic plasticity, activity-dependent long-lasting modifications that lead to increased or decreased synaptic transmission, respectively.[2] The most widely studied form of LTD depends on the activation of the NMDA-type of glutamate receptors (NMDA-LTD) and is observed at glutamatergic synapses in the CA1 region of the hippocampus.[3] The classical protocol for inducing LTD involves prolonged low-frequency stimulation (0.5–3 Hz; 5–30 min) of CA1 afferents in acute hippocampal slices. This results in a decrease of postsynaptic responses that can last for several hours. In the case of NMDAR-LTD, the decrease in synaptic strength is triggered by Ca^{2+} influx into the postsynaptic neuron through activated NMDA receptors.[4] Intracellular Ca^{2+} binds to calmodulin to activate a serine/threonine phosphatase signaling cascade involving activation of calcineurin (protein phosphatase 2B) that dephosphorylates inhibitor 1 to activate protein phosphatase 1.[5] These inductive processes rapidly lead to removal of AMPA receptors, another type of glutamate receptors, from the postsynaptic membrane. The decrease in postsynaptic sensitivity to glutamate due to AMPA receptor endocytosis is thought to be the predominant mechanism of NMDAR-LTD expression. How the activation of Ca^{2+}-dependent phosphatases is linked to the expression of LTD at the postsynaptic membrane is not clear, so far.[4]

Like in other organ systems, the function of JAK-STAT signaling in the central nervous system has been described almost exclusively as mediating the effects of cytokines, growth factors and neurotrophic proteins in the context of long-term processes like the survival and differentiation of neurons and glial cells and the regulation of cell responses to CNS lesions as well as in neurodegenerative diseases.[6-11] The study by Nicolas et al.[5] now provides evidence that activation of the JAK2-STAT3 signaling pathway is essential in the rapid induction of LTD at hippocampal synapses. By pharmacological inhibition and shRNA knockdown, they show that JAK2 activity is required for the induction of NMDAR-LTD in hippocampal slices. Inhibition of JAK2 has no effect on the expression of NMDAR-LTP nor does it interfere with the induction of other forms of synaptic plasticity. Interestingly, JAK2 can be shown to be prominently expressed in dendritic spines, the postsynaptic elements of the principal CA1 neurons. In the postsynaptic cell, JAK2 becomes phosphorylated following low frequency stimulation and this activation is mediated specifically by NMDAR, depends on the presence of Ca^{2+} and is prevented by blocking the serine/threonine phosphatases PP1 and PP2B. Again by using a battery of pharmacological tools and shRNA approaches, Nicolas et al.[1] identify STAT3 as the JAK2 substrate that is phosphorylated by low-frequency stimulation via NMDAR activation and is required for the induction of NMDAR-LTD. With these results Nicolas et al.[12] establish a new role of JAK-STAT by demonstrating that it is directly involved in activity-dependent modulation of synaptic transmission. If it can be confirmed that JAK2-STAT3 signaling is specific for one form of synaptic plasticity, tools should become available that allow for studying the contribution of NMDAR-LTD to functional plasticity of the brain and to behavioral plasticity.

A second, most intriguing finding of the study by Nicolas et al.[1] concerns the mechanism of JAK2-STAT3 signaling in NMDAR-LTD that does not involve the canonical role of STAT3 as a transcriptional regulator. Thus, induction of LTD is prevented by pharmacologically inhibiting STAT3 dimerization but is not affected when nuclear export or DNA binding of STAT3 is blocked and it does not require transcriptional activity at all. Most impressively, NMDAR-LTD can still be induced in the dendritic compartment when cell somata are mechanically removed. Together with the rapid time course of JAK2-STAT3-dependent LTD induction, these observations provide strong evidence that the function of STAT3 in the modulation of synaptic transmission in dendritic spines involves signaling mechanisms that are independent of its role as a transcription factor. Evidence is accumulating that the canonical JAK-STAT3 pathway involving nuclear translocation and DNA binding of phosphorylated STAT3 is only one of several STAT3 signaling mechanisms. Non-canonical forms of STAT3 signaling described in non-neural cells include the action of unphosphorylated STAT3 as a transcriptional regulator in the nucleus[12] and as a nucleus-independent signal influencing mitochondrial oxidative phosphorylation.[13] Cytosolic tyrosine-phosphorylated STAT3 has been localized to specific cellular compartments like focal adhesions and has been implicated in the non-translational control of cell motility.[14] The specific subcellular localizations, as observed in dendritic spines in the context of NMDAR-LTD, point to an important role for intracellular compartmentalization of JAK-STAT signaling components in defining interaction partners and signaling mechanisms.

STAT3 has also been reported to stabilize microtubules by directly binding to stathmin a microtubule-destabilizing protein[15] and, interestingly, a recent study[16] demonstrated that induction of NMDAR-LTD rapidly attenuates microtubule growth in dendrites and spines. Together with the results of Nicolas et al.,[1] these findings provide a possible link between NMDAR-LTD, activation of JAK2-STAT3 and morphological as well as functional plasticity at spine synapses. It is clear, however, that a lot of work is needed to clarify how LTD-inducing processes (Ca^{2+} influx and phosphatase activation) translate into the activation of JAK/STAT3 signaling and by which mechanism phosphorylated STAT3 contributes to reduce synaptic transmission at the synapse.

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