Complex Roles of Notch Signaling in the Development of Temporal Lobe Epilepsy: Evidence and Speculation

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The Notch pathway is well known as a master regulator of neural stem cells, but accumulating evidence suggest both novel and sophisticated roles for Notch signaling in adult brain. In the postnatal hippocampus, the regulatory function of Notch signaling on synaptic plasticity has been studied extensively. Mice with germline deletion of Notch1 or presenilins exhibited impaired long-term potentiation (LTP) and working memory, which could be understood as a consequence of disruptions in Notch-dependent neurite development and neuronal migration. Compared with long-term synaptic plasticity, recent studies have shown that Notch pathway is induced instantly by neuronal activity, suggesting a correlate of stimulus-dependent Notch activity and synaptic transmission. However, the role of those non-canonical functions of Notch signaling in neurological disorders has not been characterized so far. More recently, we have reported that Notch signaling activation led to an increase in epileptiform discharges in a mouse model of acute seizures. Temporal lobe epilepsy (TLE) is among the most frequent types of drug-resistant epilepsy, and the reorganization of neural circuits underlying the generation of recurrent seizures has been demonstrated, including impaired long-term potentiation of synaptic networks and disordered short-term synaptic responses. Here, focusing on the primary and new-emerging functions of Notch signaling, we review the complicated roles of Notch in the development of TLE and speculate some potential neuropathogenic mechanisms.

Keywords: Notch; temporal lobe epilepsy; synaptic plasticity; seizure


Notch pathway in neurogenesis

The Notch signaling has been most studied as a development pathway. Notch is a transmembrane receptor (Notch1–4 in mammals) that ligand (Jagged1/2 or Delta 1–4 in mammals) binding promotes two proteolytic cleavage events in the Notch receptor, releasing the Notch intracellular portion (NICD) that translocates to the nucleus. There, it binds RBPj and the coactivators to initiate transcription of target genes [1–5]. The canonical roles of Notch in the prenatal central nervous system (CNS) have been investigated extensively both in vivo and in vitro. In neural stem cells (NSCs), the Notch signaling maintains the self-renewal properties and inhibits neurogenesis, whereas in intermediate progenitors Notch regulates the subsequent lineage selection between neuron and glia [3]. This precise mechanism relies on the crosstalks between Notch pathway and different nerve growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (NGF) [6, 7].

Notch signaling beyond development

Because Notch pathway molecules are still expressed in adult human and mouse brain, it is no surprise that Notch signaling also play important roles in differentiated neurons [8–10]. The topic has received much attention in
the past decade, and numerous studies have indicated that Notch signaling controls neurite outgrowth [11, 12], migration of neuroblast [13, 14], dendritic branch [10, 15], and the survival of postmitotic newborn neurons [16]. Work in mouse and Drosophila has found that Notch is required for synaptic plasticity, learning, and memory. For example, transgenic NICD1 expression leads to a more complex dendritic branch both in vivo and in vitro, whereas loss of Notch1 reduces neuritis numbers [11, 12, 13]. The modulation of dendritic development by Notch pathway seems to be dependent on canonical Notch signaling, as nuclear translocation of NICD1 and the involvement of RBPj (also named as CBF1) have been confirmed in this process. In migrating neuroblasts of the developing cerebral cortex, Notch pathway interacts with reelin-DAB1 signaling to control neuronal migration and positioning [14]. Reelin signaling inhibits NICD degradation, and deficiency in either reelin or Notch leads to abnormal morphology of neuroblast that obstructs migration. Similar results have been identified in newborn granule cells of the postnatal mouse hippocampus [13]. Although in mature neurons, manipulation of Notch signaling does not affect synaptic structure, but it can continue to adjust the number of dendritic spines [17, 18]. These Notch pathway-dependent synaptic changes are probably responsible for further disruptions in neural circuits. For instance, reduction of Notch signaling caused impaired long term memory formation in Drosophila [19, 20]. Mice with null heterozygous mutations in Notch1 or RBPj exhibited similar deficits in spatial learning [21]. Down-regulated Notch signaling by a transgenic antisense Notch1 could lead to impaired LTP at hippocampal CA1 synapses [22], suggesting Notch pathway is necessary for the proper establishment of neural circuits.

However, other than the effects on building the neural networks, recent studies also involved Notch signaling in activity-dependent short-term synaptic plasticity (STSP) [23]. STSP is the ability of synapses to strengthen or weaken in their activity. Typically, outside stimuli and internal signals induce alterations in the number and combination of receptors located on a synapse [24], ion channel activity [25], the capability of vesicle pools and release of neurotransmitters [26], but without evidence of gross structural change. The process lasts from minutes to hours and thereby modulates neuronal activity.

Literature is lacking on the effects of Notch activation regarding regulation of synaptic transmission. Until recently, two groups have provided a little evidence that Notch signaling is closely related with STSP. Gaiano and his colleagues reported that Notch signaling was activated by neuronal activity [27], as indicated by an increase in Notch1 expression and cleaved NICD1 in cultured hippocampal neurons stimulated with N-methyl-D-aspartate (NMDA). They also showed Notch1 and Jagged1 were present at the rodent synapse which co-located with PSD95 and synapsin, respectively. Furthermore, the activity-regulated gene Arc is an upstream regulator of Notch cleavage, and both proteins physically interact with dynamin, which is critical for the generation of synaptic vesicles [28]. Struhl and his colleagues showed that Notch signaling in Drosophila was activated specifically by odor stimulation in brain regions responsible for olfactory processing, and another Notch ligand Delta was the upstream regulator [29]. These findings provided the first evidence that the time scale of Notch response can be occurred within hours (NICD1 increased 1.5 h after NMDA treatment). Although still incompletely understood, it seems likely that Notch pathway is involved in activating neuronal excitability in response to stimuli and that it potentially has regulatory function in endocytic trafficking.

Notch signaling in the epileptic hippocampus

The essential role of Notch in neural development is demonstrated by its implication in CNS diseases such as stroke, Alzheimer's disease and Glioma [30]. However, the role of Notch signaling beyond regulating NSCs maintenance and differentiation is still poorly understood, and its implication for human disease is yet to be proven. Our recent study found that Notch signaling was involved in the generation of acute seizures, the first proof for the effects of Notch-dependent STSP in human disease, as far as we know [31].

Temporal lobe epilepsy with hippocampal sclerosis is a complex disease of various neuropathologic features [32], most of which are potentially relevant to Notch functions (see Fig.1 and discussion below). Aberrant synaptic reorganization after seizures is quick and progressive. Decreased GABA receptors, activation of excitatory receptors, and disrupted synaptic structures including mossy fiber sprouting and the generation of granule cell basal dendrite, all of these changes contribute to the development of chronic epilepsy [33]. Our previous study examined the spatio-temporal expression of Notch signaling in the hippocampus after kainic acid(KA) induced status epilepticus [31]. Consistent with the finding that Notch was activated in response to NMDA stimulation [27], seizures themselves could increase Notch activity. Notably, Notch activity was still up-regulated even in latent and chronic stages of temporal lobe epileptogenesis. We also observed a shift expression of Notch1 and Jagged1 from pyramidal neurons of normal hippocampus to ectopic granule cells of the sclerotic hippocampus. Similar pattern of Notch activation was found in the hippocampal specimens from subjects with
mesial TLE. Importantly, this distinctive pattern of Notch signaling activation changes was restricted to the dorsal hippocampus ipsilateral to the injection.

Using an acute model of seizures, we found that activation of Notch dramatically influenced epileptiform discharges. Moreover, the glutamatergic synaptic responses of CA1 pyramidal neurons were changed in response to Notch activation or inhibition. Alberi et al. provided the evidence of activity-dependent Notch signaling in CA1 pyramidal neurons [27], and our study in TLE supports this feature and proposes an involvement of aberrant Notch signaling in promoting acute seizures. That is to say, Notch signaling activation in response to neuronal activity is likely to play a positive feedback role that facilitates neurotransmission. Furthermore, DAPT treatment in cultured hippocampal neurons blocked the generation of synaptic vesicles, suggesting that Notch pathway plays a role in the regulation of endocytic machinery. Given the fact that endocytosis is indispensable for the surface expression of Notch and its ligand [34, 35], the generation of synaptic vesicles is a promising model to explain how Notch pathway participates in regulating STSP. Moreover, in contrast to glial cells that are closely related to the initial mechanisms underlying seizure generation [36, 37], intervention of Notch signaling has no effect on the onset of KA induced acute seizures. This is consistent with the common idea that aberrant signaling pathways in microglia and astrocyte are likely to be the trigger [38, 39].

Interestingly, activated Notch signaling in synapse of dispersed granule cells seems to execute an opposite function. Our unpublished data have identified that Notch activation by exogenous Jagged1 in the sclerotic hippocampus has anticonvulsant effects, suggesting other factors are involved in determining which response, positive or negative, Notch signaling should carry on. On the basis of complicated activation patterns of Notch signaling in TLE, it seems clear that continuous administration of DAPT to inhibit Notch activation during the development of TLE is neither a suitable method to study Notch nor a possible way for therapy. Cre/loxP and viral gene transduction technologies must to be applied in future works. Although these observations make the role of Notch signaling in the epileptic hippocampus become more sophisticated, after all, Notch itself is one among the best cell-type specific regulator.

The functions of Notch signaling in CNS are also in line with other neuropathologic changes during the development of TLE. Seizure is characterized by hypersynchronous neuronal firing and it strikingly damages NSCs [40], the same situation is often observed in stroke [41]. Notch activity was disturbed in NSCs of subgranular layer of the dentate gyrus as demonstrated by reduced Hes5 (a downstream effector of Notch), the authors suggest that it possibly coupled with an enhanced differentiation into astrocytes [42]. Imbalanced expressions of other factors in neuronal proliferation and survive such as cdk5 and NF-KB have also been observed in TLE and potentially link with Notch pathway [43-45]. In addition, several studies have provided evidence of impaired Reelin signaling in contributing granule cell dispersion [46, 47]. As mentioned above, Notch molecules serve as downstream effector of Reelin that maintains radial glial cells in the rodent dentate gyrus. Therefore, it is interesting to speculate that disrupted interaction between Notch and Reelin pathway could be associated with the occurrence of dentate gyrus dispersion. The crosstalk of Notch and mTOR pathway has recently been identified in cancer cells. Activation of mTOR pathway arouses Jagged1-Notch signaling, and consequently promotes cell proliferation [48, 49]. In TLE, the mTOR has become a promising therapeutic target because rapamycin (a mTOR inhibitor) could prevent mossy fiber sprouting in TLE rodent models, and has anti-epileptogenic effects [50-52]. The mTOR pathway is of great importance for synaptic plasticity and memory [53], consistent with what has been confirmed as one of Notch functions. Since both Notch and mTOR signaling are activated during temporal lobe epileptogenesis, it is reasonable to speculate that Notch may collaborate with mTOR to play a role in synaptic dysfunction. Increasing evidence supports the involvement of inflammatory and immune processes in the pathogenesis of seizures [54]. Toll like receptors (TLR) are a class of proteins that play a key role in the innate immune system [55]. TLR4 has been reported to mediate neuronal excitability in TLE.
Although TLR stimulation acts as an upstream activator of Notch signaling in macrophage \(^{[6]}\), the evidence for Notch functions in CNS glial cells is still lacking, and whether Notch signaling is involved in the process needs further studies.

The efforts to understand the role Notch pathway plays in adult brain and disease requires detailed knowledge of how the “on” and “off” states of such signaling are brought about. Unfortunately, the mechanism of Notch signaling being up or down regulated is still poorly known. Given the comprehensive functions of Notch signaling in regulating neurons from infancy to old age, further studies will try to provide more information necessary to bridge the gaps in our understanding of the multiple and complex roles of abnormal Notch signaling in TLE.

Conflict of Interest

The authors declare that there is no competing interests.

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