Molecular and Cellular Neuroscience 81 (2017) 64–71

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

Role of the adhesion molecule F3/Contactin in synaptic plasticity and memory

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ARTICLE INFO

Article history:
Received 13 August 2016
Revised 7 December 2016
Accepted 22 December 2016
Available online 28 December 2016

Keywords:
Cell adhesion molecules
F3/Contactin
Synaptic plasticity
Long-term potentiation
Memory
CREB
Aging
Beta-amyloid
Alzheimer's disease

ABSTRACT

Cell adhesion molecules (CAMs) have a pivotal role in building and maintaining synaptic structures during brain development participating in axonal elongation and pathfinding, glial guidance of neuronal migration, as well as myelination. CAMs expression persists in the adult brain particularly in structures undergoing postnatal neurogenesis and involved in synaptic plasticity and memory as the hippocampus. Among the neural CAMs, we have recently focused on F3/Contactin, a glycosylphosphatidyl inositol-anchored glycoprotein belonging to the immunoglobulin superfamily, involved in neuronal development, synaptic maintenance and organization of neuronal networks. Here, we discuss our recent data suggesting that F3/Contactin exerts a role in hippocampal synaptic plasticity and memory in adult and aged mice. In particular, we have studied long-term potentiation (LTP), spatial and object recognition memory, and phosphorylation of the transcription factor cAMP-Responsive-Element Binding protein (CREB) in a transgenic mouse model of F3/Contactin overexpression. We also investigated whether F3/Contactin might influence neuronal apoptosis and the production of amyloid-beta peptide (Aβ), known to be one of the main pathogenetic hallmarks of Alzheimer's disease (AD). In conclusion, a further understanding of F3/Contactin role in synaptic plasticity and memory might have interesting clinical outcomes in cognitive disorders, such as aging and AD, offering innovative therapeutic opportunities.

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1. Synaptic plasticity and memory: a brief introduction

Synaptic plasticity is a critical phenomenon in both developing and adult nervous system ensuring the essential structural and functional changes in a complex dynamic system such as the brain. In fact, the ability to acquire and store new information is essential for the survival of complex organisms. Storage processes require formation of new synaptic connections triggered by proper changes in synaptic activity, which, in turn, needs morphological modifications in order to become permanent.

These adaptive structural and functional changes have been widely studied in the last 60 years to unravel the multifaceted mechanisms underlying synaptic plasticity. In the late forties, the "Hebbian theory" was proposed to explain neuronal communication (Konorski, 1948; Hebb, 1949), later elegantly resumed as "neurons wire together if they fire together" (Löwel and Singer, 1992; Shatz, 1992), indicating that functional changes in activity require structural changes in synapses to achieve long lasting memory formation. Interestingly, activity-dependent

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http://dx.doi.org/10.1016/j.mcn.2016.12.003
1044-7431/

neuro- and synapto-genesis have been observed in several adult brain areas where new neurons and synapses are able to integrate with the pre-existing structures without altering the latter basal functions (for a review see Kelsch et al., 2010).

In this context, one of the most studied areas has been the hippocampus, a structure within the temporal lobe, proved to be fundamental for learning and memory. Indeed, although the final storage of information is thought to be located in neocortical areas (Wiltgen et al., 2004), memory consolidation processes seem to be sensitively dependent from the integrity of hippocampus, as observed in patients with damage of this structure who exhibited severe dysfunction in acquiring new memories (Scoville and Milner, 1957; Milner, 2005). Interestingly, during learning hippocampus physiologically exhibits a peculiar pattern of activity, defined as theta waves (Greenstein et al., 1988; For a review see Hasselmo, 2005), thought to facilitate the memory formation processes. At cellular level, this is one of the mechanisms of activation able to induce persistent changes in neuronal activity leading to a long-lasting increase, i.e. long-term potentiation (LTP) in the efficacy of synaptic transmission (Bliss and Lomo, 1973). A compelling amount of data has been collected emphasizing the physiological significance of LTP that is now thought to represent the molecular correlate of learning and memory (Lynch, 2004). In particular, LTP, like memory, exhibits a protein-synthesis independent early phase (E-LTP), and a protein-synthesis dependent late-phase (L-LTP) underpinned by different mechanisms. These modifications of synaptic efficacy might involve both the pre- and post-synaptic machinery, involving an increase of neurotransmitter release or a different sensitivity of the post-synaptic neuron to the neurotransmitter. In general, it is widely accepted that short-term modifications are mainly caused by post-translational modifications of existing proteins (i.e. receptors, ion channels), whereas long-term changes require transcription and synthesis of new proteins leading to structural changes of the synapses. Thus, L-LTP as long-term memory requires a modification of gene expression. One of the key molecules involved in the regulation of gene expression in response to neuronal activity is represented by the nuclear transcription factor cAMP-responsive element binding protein (CREB). CREB regulates the expression of several genes playing a crucial role in in development, cell proliferation and differentiation, synaptic plasticity and memory (for reviews see Lonze and Ginty, 2002; Puzzo et al., 2016). As regards the subject of this review, CREB role in synaptic plasticity and memory has been widely demonstrated by gain or lack of function studies. In the early 90's three important manuscripts reported the key role of CREB in long-term plasticity and memory, demonstrating that: i) microinjections of CRE sequence into the nucleus blocked CREB function with a consequent inhibition of the long-term increase in synaptic strength (Dash et al., 1990); ii) the expression of a dominant-negative CREB transgene in Drosophila inhibited long-term memory (Yin et al., 1994); iii) CREB knock out mice presented an impairment of long-term plasticity and memory (Bourtchuladze et al., 1994). In the following years, several evidence have been collected supporting the idea that CREB is required for memory formation (Barco and Marie, 2011; Kandel, 2012). Now, we are aware that several molecular pathways might act at pre- and post-synaptic levels to induce long-lasting modification of synaptic strength and that both functional and structural modification are needed to let the new information be persistent. However, it is still a challenge for the neuroscience community to untangle the complex mechanisms underlying such a dynamic process as plasticity. How do transient modifications of synaptic strength become long-lasting? How do synaptic structural and functional changes correlate with memory?

2. Cell adhesion molecules in synaptic plasticity and memory

Cell interactions are known to play a key role in neural developmental events and in particular in building and maintaining synaptic structure and function (Melom and Littleton, 2011). Although these events are mostly relevant for development, they also occur in adult nervous tissue (Kolodkin and Tessier-Lavigne, 2011), and in both cases they correlate with the expression of cell adhesion molecules (CAMs) (Gerrow and El-Husseini, 2006; Margeta and Shen, 2010; Stagi et al., 2010). Thus, CAMs might be the molecular actors needed to mediate adhesive cell-cell and cell-matrix interactions in order to stabilize the synapse and ensure the required structural and functional changes during plasticity.

Neural CAMs comprise the cadherin, integrin and immunoglobulin superfamily (IgSF) that have been demonstrated to participate in initiating and maintaining synaptic changes during LTP and memory. For a summary of CAMs effects on synaptic function and memory, see Table 1.

Integrins are proteins mediating the interaction between cells and the extracellular matrix (Harburger and Calderwood, 2009). Interestingly, they function as receptors for extracellular ligands and are able to transmit signals bidirectionally, i.e. from the cell to the extracellular matrix e viceversa. Their role in synaptic plasticity, especially LTP consolidation, has been demonstrated by several studies (for a review see McGeachie et al., 2011), mainly performed with lack of function approaches by using the Arg-Gly-Asp (RGD) sequence needed for integrins binding, antibodies, or mutant deficient models. Inhibition of integrin function by the RGD peptide induced an impairment of CA1 hippocampal LTP stabilization (Xiao et al., 1991; Stäubli et al., 1998). Infusion of integrin blocking antibodies induced an impairment of hippocampal LTP similar to that obtained with RGD peptides (Chun et al., 2001; Kramár et al., 2006). RGD application also increased the number and length of dendritic spines in cultured hippocampal neurons whereas the use of anti-integrin antibodies partially blocked these effects (Shi and Ethell, 2006), suggesting that integrins are involved in the structural changes associated with LTP. Other than LTP, integrins might play a role in basal synaptic transmission (Kramár et al., 2003), neurotransmitter release probability (Huang et al., 2006) and some forms of short-term plasticity. Indeed, the inhibition of integrins abolished the stretch-induced enhancement of neurotransmitter release at motor nerve terminals (Chen and Grinnell, 1997). Moreover, the disruption of Volado, a gene encoding for two forms of the α-integrin, impaired olfactory associative short-term memory in Drosophila, whereas expression of an integrin subunit rescued the memory deficit (Grotewiel et al., 1998). The use of mutant mice allowed to further demonstrate that integrins are involved in synaptic plasticity but also hippocampal-dependent spatial memory and working memory (Chan et al., 2003, 2006, 2007). In rats, hippocampal expression of integrins highly correlated with memory performance in an inhibitory avoidance task (Huang et al., 1998).

Cadherins are also known to play a role in synapse formation and function (for a review see Tai et al., 2008). They are expressed both in pre- and post-synaptic terminals during development and they persist in adult life, where they regulate structural synaptic changes, such as dendritic spine morphogenesis (Togashi et al., 2002; Elste and Benson, 2006) and AMPA receptor trafficking (Nuriya and Huganir, 2006).

It has been demonstrated that blocking cadherin function by antibodies or peptides affected the induction of hippocampal LTP and E-LTP (Tang et al., 1998; Yamagata et al., 1999), whereas results on basal synaptic transmission are controversial. An impairment of presynaptic short-term plasticity has also been found in cadherin null mice (Jüngling et al., 2006). The role of cadherins in memory is less clear. For example, mice lacking hippocampal cadherin 11 showed altered anxiety but not spatial memory (Manabe et al., 2000), whereas mice lacking specific catenins, a family of proteins forming complexes with cadherins, exhibit deficits in CA1 LTP and memory (Park et al., 2002; Israely et al., 2004).

Among neuronal CAM, IgSF are widely studied for their role in neuronal development, as well as synaptic formation and maintenance (Yamagata et al., 2002; Dalva et al., 2007; Milanese et al., 2008; Yamagata and Sanes, 2008; Boutin et al., 2009; Barry et al., 2010; Wanner et al., 2011). CAMs IgSF expression persists in the adult brain, especially in structures undergoing postnatal neurogenesis and