REVIEW

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The role of DSCAM in the regulation of synaptic plasticity: possible involvement in neuropsychiatric disorders

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Synaptic plasticity simply put, is the activity-dependent modification of the strength or efficacy of synaptic transmission in the network of synapses in the brain. The role of synaptic plasticity in disease is an active area of research. Changes in plasticity translate to the release of neurotransmitters at the synapse and subsequently, the way humans see the world. It is known that neuropsychiatric disorders such as depression, posttraumatic stress disorder (PTSD), and Alzheimer's disease (AD) are related to pathological changes in dynamic processes in synapses, dialogue between neurons, and finally, changes in overall plasticity. To find a cure for these plasticity related diseases, it is imperative that we understand the precise mechanisms that perturb the homeostatic balance leading to the disease state. The aim of this review is to present what is currently known about DSCAM (Down Syndrome Cell Adhesion Molecule) a protein that is directly connected to pathological changes in synaptic plasticity. The review will present information on DSCAM and how it is connected to glutamate (Glu) and γ-Aminobutyric acid (GABA) neurotransmission pathways. Finally, the review throws some light on the possible involvement of DSCAM in a spectrum of psychiatric disorders apart from Down syndrome (DS).

Key words: DSCAM, Glu, GABA, synaptic plasticity, Down syndrome, mood

INTRODUCTION

In 1949, Donald Hebb postulated that strong interactions existed between communicating synapses, a remark often presented as: "Fire together, wire together" (Hebb 1949). Synaptic plasticity is a language of neuronal communication and depends on timing, the strength of pre- and postsynaptic dialogue, and the structure of dendritic spines (Cramer and Galdzicki 2012, Dan and Poo 2006). The process of synapse strengthening involves several factors, including the formation of new dendritic spines, modification of existing synapses through receptor variation, silent synapse activation, changes in the size or shape of the synapse, and changes in the timing and levels of neurotransmitter release (Kossut 2007). The number of spines, their localization, and the shape of individual spines are important factors in this process (Alves-Sampaio et al. 2010). Any disruption to this communication path results in the reduction of potential sites for the occurrence of plasticity (Cramer and Galdzicki 2012).

Cell Adhesion Molecules (CAMs) are known participants in the process of forming synaptic connections, together with other cell surface recognition molecules they take part in the processes of homophilic and heterophilic bindings, fasciculation, and defasciculation (Hattori et al. 2008). Down Syndrome Cell Adhesion Molecule (DSCAM) is an important factor in the process of synapse strengthening and the timing of synaptic dialogue transmission (Li et al. 2009). Often, synapse dialogue is discussed in terms of long-term potentiation (LTP) and/or long-term depression (LTD). LTP is a long-lasting enhancement of synaptic efficacy and is a predictor of synaptic plasticity, as well as a learning and memory sensor. Both processes are strictly linked to glutamate (Glu) activation.

Pathological changes in the dynamic processes that occur at synapses coupled with neurotransmission shifts

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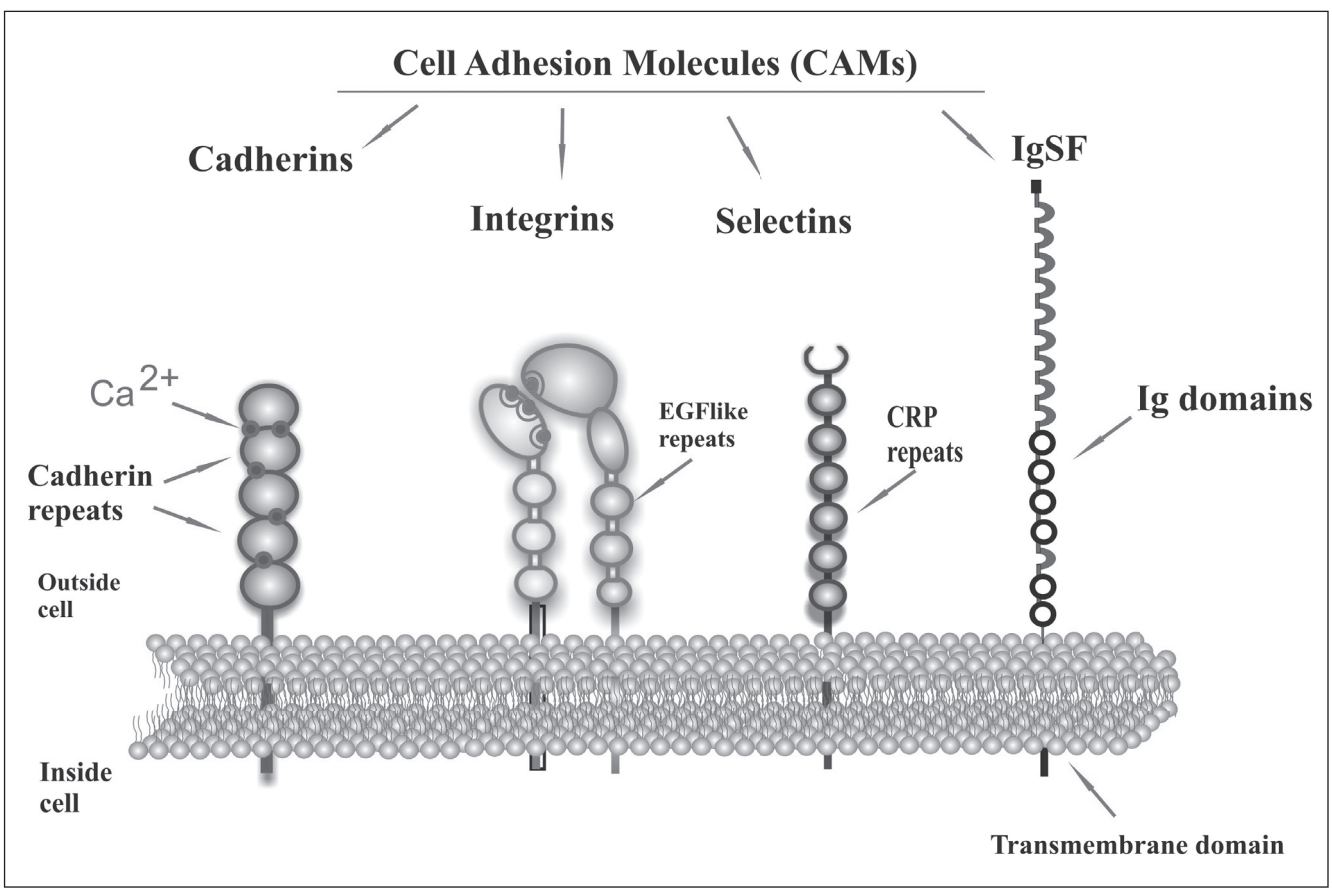
are characteristic features of many neuropsychiatric diseases. In addition, characteristic changes in DSCAM levels are observed. Although DSCAM plays unquestionable roles in the different steps of neural circuit formation (Alves-Sampaio et al. 2010), dendritic tree formation and synaptogenesis (Hortsch and Umemori 2009, Jia et al. 2011, Pérez-Núñez et al. 2016, Schmucker and Chen 2009, Zhu et al. 2006), the more interesting questions to ask are: 1) How does this knowledge help us in understanding synaptic plasticity and its role in the pathophysiology of neuropsychiatric disorders? 2) Is the DSCAM protein/gene only an "observer" of the changes in equilibrium, or an active player? To accurately answer these questions, we need to have a precise view of all changes that take place in Down syndrome (DS) – the best model of disturbed plasticity and learning potential, with a characteristic decrease in dendritic branching and spine density in the hippocampus and cortex in parallel to overexpressed DSCAM (Alves-Sampaio et al. 2010, Ferrer and Gullotta 1990, Sterne et al. 2015).



Function			
Cadherins	Integrins	Selectins	IgSF
– surface glycoproteins – calcium dependent – cell-cell adhesion – tissue patterning – cancer	– heterodimers – transmembrane linkers: extracellular matrix and actin cytoskeleton	– first step of adhesion – the attachment of leukocytes to the wall L-selectins are expressed on circulating leukocytes P-selectins – on endothelial cells and granules of platelets E-selectins – induced by IL-1, LPS, TNF on vascular endothelial cells	– cell surface receptors and cell adhesions DSCAM NCAMs ICAMs VCAMs PECAM-1 ESAM – function mainly in the immune system – cell-cell reorganisation

(Kourtidis et al. 2017, Bajnok et al. 2017, Springer 1994, Alberts et al. 2002, Harpaz and Chothia 1994, Giancotti and Ruoslathi 1999, Wong et al. 2012).

Fig. 1. Classification and function of Cell Adhesion Molecules (CAMs).

DSCAM – a Down Syndrome Cell Adhesion Molecule

The DSCAM gene is located on human chromosome 21 (21q22.2–q22.3), which is strictly associated with DS (Edelman and Crossin 1991, Head et al. 2007, Yamakawa et al. 1998). A second DSCAM gene is located on chromosome band 11g23 (DSCAML1), where it is associated with Tourette's syndrome (Agarwala et al. 2001). DSCAM belongs to the immunoglobulin superfamily of cell adhesion molecules (Ig-CAMs) (Yamakawa et al. 1998) and is a cell surface transmembrane receptor (Hortsch and Umemori 2009). Cell adhesion molecules (CAMs) mediate cell-to-cell and/or cell-to-extracellular matrix interactions and are predominantly classified as integrins, selectins, cadhedrins and the immunoglobulin superfamily (IgSF) (Wong et al. 2012). Besides DSCAM, other IgSF members include: NCAM (Neural Cell Adhesion Molecule, CD56), ICAM (Intracellular Adhesion Molecule, CD54), VCAM (Vascular Cell Adhesion Protein 1) and PECAM-1 (Platelet Endothelial Cell Adhesion Molecule, CD31) (Wong et al. 2012), (see Fig. 1 for classification and function of CAMs).

DSCAM is one of the largest IgSF proteins (220kDa); it is composed of an N-terminal signal peptide, 10 immunoglobulins (Igs) and 6 fibronectin type III (FNIII) domains, a transmembrane domain (TM) and a cytoplasmic tail (Hortsch and Umemori 2009, Jin et al. 2013, Yamakawa et al. 1998). The tenth Ig domain is separated by the fourth and fifth FNIII domains. The domain structure composition of DSCAM is truly unique and differentiates it from other members of the IgSF (Hortsch and Umemori 2009). A single membrane-spanning domain links the extracellular domain with the cytoplasmic fragment of DSCAM (Hortsch and Umemori 2009). The cytoplasmic fragment of DSCAM is composed of 300-400 amino acids with high level of tyrosines serving as a binding site for the SH2 domain of dedicator of cytokinesis (Dock) proteins or the postsynaptic density protein (PDZ) domain binding-site (Hortsch and Umemori 2009) (Fig. 2).

DSCAM transcripts are subject to alternative splicing and therefore can generate various tissue-specific protein isoforms (Hortsch and Umemori 2009). DSCAM was found in the neurons of the central nervous system (CNS) and peripheral nervous system (PNS) during the mouse developmental period. Precisely, DSCAM expression was detected in tissues such as the liver, lungs, limb, and buds only during the developmental period (Agarwala et al. 2001). It is equally expressed in the cortex, olfactory bulb, dentate gyrus, hippocampus (CA1, CA3), thalamus, and cerebellum of the adult mouse brain (Agarwala et al. 2001). More precisely, DSCAM receptors were found on the dendrites and axons of neurons (Hortsch and Umemori 2009). DSCAML1 shows differential expression patterns compared to DSCAM during development and in adult mice, e.g. DSCAM shows strongest expression in the pyramidal neurons of the cortex layers 3 and 5 (Barlow et al. 2002).

Both forms of DSCAM are expressed in the hippocampus (with higher expression in the dentate gyrus and Ammon's horn) and in the olfactory bulb (Barlow et al. 2002). Apart from its expression in the brain of adult mice, DSCAML1 is also expressed in tissues such as the heart, spleen, lungs, kidneys, and testis (Barlow et al. 2001, Barlow et al. 2002). In humans, both DSCAM and DSCAML1 are expressed in the hippocampus, amygdala, thalamus, caudate nucleus, and corpus callosum (Barlow et al. 2002, Yamakawa et al. 1998). Overexpression of DSCAM has also been documented in the brains of human patients with DS (Bahn et al. 2002, Head et al. 2007, Sterne et al. 2015). Saito et al. (2000) reported the presence of DSCAM in the cerebellar white matter of control and DS patients and suggested DSCAM may play a role in regulating myelination.

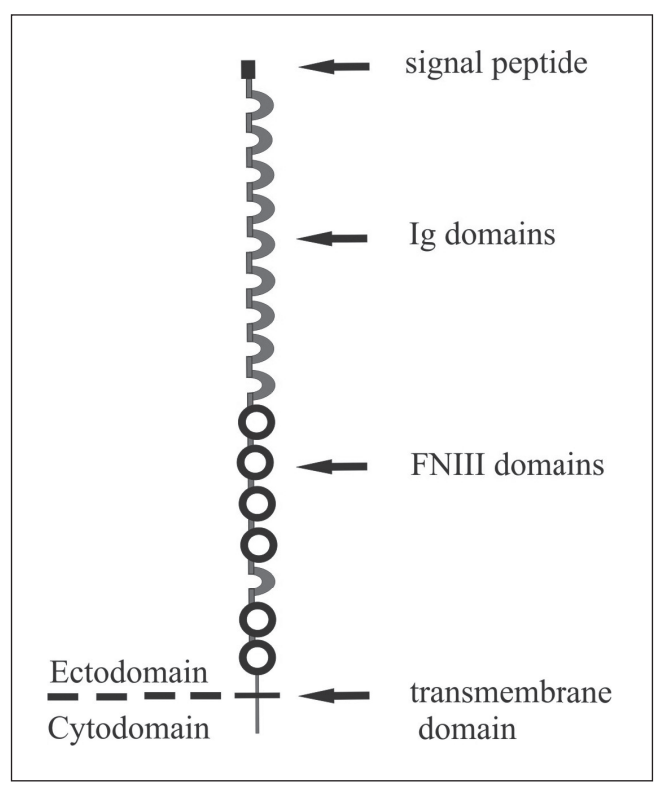


Fig. 2. Structure of DSCAM.

DSCAM is a transmembrane receptor, Ig-CAM protein. The Structure of DSCAM is composed of 10 Ig domains, and 6 fibronectin type III (FN III) domains, tandemly arranged. The DSCAM family consists of 2000 amino acids, with an average molecular weight of 220kDa. Extracellular domain units are connected with the cytoplasmic region of DSCAM by a membrane-spanning domain. DSCAM cytodomains contain various tyrosines, which are binding sites for i.e. Src Homology 2 (SH2) domain (Docks) and PDZ domain-binding (Hortsch and Umemori Eds 2009).

Although DSCAM has been shown to be essential in the organization of the nervous system, dendritic tree formation and synaptogenesis (Hortsch and Umemori 2009, Jia et al. 2011, Pérez-Núñez et al. 2016, Schmucker and Chen 2009, Zhu et al. 2006), some controversy still exists in the field concerning its role in the CNS. The paragraphs that follow will attempt to shed more light on its role in the CNS based on its role in DS and non-DS conditions. Furthermore, its connection with major neurotransmission pathways will be discussed.

DSCAM in DS and other conditions

Down syndrome

DS is an outcome of trisomy of human chromosome 21, the most common reason of genetic mental retardation (Alves-Sampaio et al. 2010, Antonarakis et al. 2004). Although a considerable amount of individual variability exists in persons with DS, they exhibit a characteristic intellectual disability, with decreased IQ score and speech problems that get worse during aging (Hickey et al. 2012, Weijerman and Winter 2010). Morphologically decreased brain size, aberrant gyrification, and disturbed neurogenesis are also observed (Lockstone et al. 2007, Mrak and Griffin 2004). As an outcome of reduced brain size, reduced volumes of cerebral gray and white matter are observed (Pinter et al. 2001). At the same time, larger subcortical and parietal gray matter and temporal white matter are present, which according to Pinter et al. (2001) may be the cause of verbal memory deficits, and changes in short-term visuospatial memory. Cognitive deficits in DS persons comprise of long-term memory changes and difficulty in the assimilation of new skills (Pennington et al. 2003, Yu et al. 2010).

In DS persons, dendritic branching and spine density are diminished both in the hippocampus and cortex (Alves-Sampaio et al. 2010), with changes in the morphology and volume of these structures. Ferrer and Gullotta (1990) reported a 15% decrease in DS hippocampal spines. Similar morphological changes have also been reported in mouse models of DS (Ts65Dn and Ts1Cje mice). Both models show similar phenotypes and characteristic morphological changes, although obtained by different chromosomal manipulations. Because this is not a major focus of this study, readers can review Olson et al. (2004) or Belichenko et al. (2015) for detailed information on both models.

Decreased spine densities and increased spine volumes in the neocortex and hippocampus were found in the Ts65Dn mouse model of DS (Belichenko et al. 2004, Siarey et al. 2006).

Furthermore, specific presynaptic bouton enlargements and the presence of a great number of vacuoles and multivesicular bodies in spines were found in Ts65Dn mice (Belichenko et al. 2004). Characteristic changes in hippocampus inhibitory synapse position from shafts onto the necks of dendrites were also documented in these mice (Belichenko et al. 2004, Cramer and Galdzicki 2012). Deficits in cognitive tests were found to be linked to reduced hippocampal volumes (Cramer and Galdzicki 2012). Furthermore, exaggeration of inhibition in the trisomic hippocampus was documented (Ts65Dn) (Cramer and Galdzicki 2012). In a parallel study, Alves-Sampaio et al. (2010) showed that DSCAM plays a functional role in dendritogenesis and synaptic plasticity. Using a plasmid encoding DSCAM-IRES-GFP, the authors showed significantly reduced neurites crossing, using Sholl morphometric analysis, and reduced total dendrite length in hippocampal DSCAM-overexpressing neurons. Furthermore, the hippocampus of Ts1Cje mice had increased levels of DSCAM mRNA and protein (Alves-Sampaio et al. 2010).

Mood related disorders

Neuronal atrophy and cognitive deficits are also known characteristics of depression and other stress-mediated disorders (Yu et al. 2011). Stress-mediated changes in neuroplasticity in the dentate gyrus have been proposed to play significant roles in the pathophysiology of depression, despite some critical reports (Liu et al. 2017). Reductions in dendrite arborization and spine density have been reported in the cortex of postmortem brains of depressed patients (Banasr et al. 2011, Rajkowska and Miguel-Hidalgo 2007). Early life stress is an accepted factor in producing neuropsychiatric changes during adolescence, as well as being linked to reduced dendritic length, branching, and spine density in the limbic structures and prefrontal cortex (Brenhouse and Andersen 2011, Lupien et al. 2009). Loss of spines and withdrawal of dendrites of pyramidal neurons of the prefrontal cortex in rodents is common in chronic stress (Banasr et al. 2011, Radley et al. 2004). Importantly, antidepressant drugs are effective as neuroplasticity enhancers (Banasr et al. 2011, Eyre and Baune 2012). Furthermore, Amano et al. (2008) found an association between increased DSCAM expression and bipolar disorder in a gene screen of patients with bipolar disorder (manic-depressive disorder). Postmortem examination of brains from bipolar subjects carrying the G allele of DC141 SNP, showed elevated levels of DSCAM (Amano et al. 2008).

Posttraumatic stress disorder (PTSD)

Results obtained in the screen of genes in the glucocorticoid receptor (GR) pathway and genes of the neural stress response in PTSD patients (male veterans), found low levels of expression of DSCAM in the test group compared to controls (Logue et al. 2015). Interestingly, a parallel decrease in BDNF expression was also observed in these patients (Logue et al. 2015). It is very interesting to note that DSCAM is downregulated in PTSD, where individuals may not forget the traumatic events in their lives.

Alzheimer's disease (AD)

Mental retardation presents the direct opposite of PTSD with an upregulated level of DSCAM. Dementia is not uncommon after 20-years or later in the life of DS persons (Myers and Pueschel 1991). Some DS persons develop AD with dementia later in life; while some have evidence of AD neuropathology but may not develop dementia (Head et al. 2007). Chromosome 21 links DS with familial AD (St George-Hyslop et al. 1987). DS is a result of trisomy 21, with triplication of other genes, e.g. the APP gene, leading to increased Amyloid-β (Aβ) levels in the brain, which is a characteristic neuropathology of AD (Doran et al. 2017). In familial early-onset AD, a duplication of the APP genomic locus may occur that is known as partial trisomy of chromosome 21 (PT21), with absence of the clinical symptoms characteristic of DS (Doran et al., 2017, Sleegers et al. 2006).

Doran et al. (2017) suggests that APP is critical to the pathogenesis of AD in DS, as DS patients normosomic for APP showed very slow cognitive loss. Imaging studies using PET suggest compensatory increases in metabolic

Table I. Main changes observed in Down syndrome, Alzheimer disease, depression and PTSD – comparative study.

	Down syndrome	Alzheimer disease	Depression	PTSD	References
			A		
DSCAM	↑ protein/human/ brain	↑ APP transgenic mice/brain/gene/ protein	↑ (bipolar)serum and postmortem brain/ human/gene	↓ gene/human/ blood	(Saito et al. 2000, Jia et al. 2011, Amano et al. 2008, Logue et al. 2015)
Spine density/ dendritic branching	↓ spine numbers/ Ts65Dn ↑ mice/Hp spine heads/Hp	↓ dendritic spines/ Hp/Cx	↓ rats dendric spine density Hp (CA1,CA3); DG	↓ PTSD patients/mice (type-dependent)	(Kurt et al. 2004, Chen et al. 2012, Dorostkar et al. 2015, Norrholm and Ouimet 2001, Madder 2017, Young et al. 2015)
Cortico -sterone	↑ Ts65Dn mice large group housing	↑ Hp culture	↑ human/serum	↕ PTSD ↔ patients/mice	(Martínez-Cué et al. 2005, Wuwongse et al. 2013, Pariante and Lightman 2008, Madder 2017, Otte et al. 2005)
			B		
LTP	↓ Hp/Ts65Dn	↓ Hp/APP mice/ human Cx	↓ rats/Hp	↑ biphasic/Hp/Am/ rats	(Siarey et al. 1999, Chapman et al. 1999, Koch et al. 2012, Liu et al. 2017, Akirav and Richter-Levin 1999)
Glu	↔ fetus/Cx	↓ Human/Cx/ HPLC Reuptake Hp	↑ (bipolar/MDD) Fcx	↑ Hp/rats Am/Hp/human	(Whittle et al. 2007, Gueli and Taibi 2013, Zhang et al. 2016, Li et al. 2011, Hashimoto et al. 2007, Gao et al. 2014, Friedman et al. 2014)
GABA	↓ fetus/Cx	↓ Human/Cx/ HPLC ↑ Hp/HPLC/ Astrocytes	↓ (bipolar)serum human	↑ Hp/rats	(Whittle et al. 2007, Gueli and Taibi 2013, Li et al. 2016, Petty et al. 1993, Gao et al. 2014)

↑↓ increase, decrease, ↕ different results – increase and decrease, ↔ no difference or difficult to assess.
Hp – Hippocampus, Am – Amygdala, Cx – Cortex, DG – Dentate Gyrus, FCx – Frontal Cortex, PTSD – Post Traumatic Stress Disorder, Ts65Dn – mouse Down Syndrome model, APP – mouse Alzheimer's Disease model.

rate in vulnerable brain regions in DS prior to the development of dementia (Head et al. 2007). In fact, Head et al. (2007) found DSCAM localization in cores and peripheral fibers linked to senile plaque formation in DS with AD. Amyloid precursor protein (APP) transgenic mice (a model of AD) showed a significantly higher level of DSCAM expression in the cerebral cortex, compared with the control wild-type group (Jia et al. 2011). It was speculated that the observed effect was a leading cause of learning, memory, sensory perception and voluntary movement deficits in APP transgenic mice (Jia et al. 2011). In the mouse model of AD (APP transgenic mice), the DSCAM level was found to progressively increase with age (Jia et al. 2011). However, APP and DSCAM associations seen both in DS persons and AD models should be considered as more complex than additive effects of potentially overexpressed proteins. Since AD mouse models show microglial and astrocytic activation, with increased levels of cytokines and cyclooxygenase-2 (COX-2) (Birch et al. 2014), while DSCAM represents an IgSF member (Wong et al. 2012), implication of the inflammatory response should be considered in that context. In fact, our data found engagement of COX-2 in the regulation of DSCAM levels in the mouse brain (unpublished data).

The proportion of DSCAM, corticosterone levels and changes in spine density in DS and neuropsychiatric disorders discussed above are shown in Table IA. Because changes in plasticity are strictly linked to fluctuations in interactions between neurotransmitters, including transcriptional and translational changes, the remainder of the review will focus on such signaling pathways, with particular attention to the involvement of DSCAM.

Glutamate, GABA and DSCAM expression

Studies on DSCAM and its interaction with neurotransmitters are mostly based on animal models. Li et al. (2009) suggested that Dscam-mediated signaling was substantially involved in Glu receptor changes. Using the *Aplysia* culture model, Li et al. (2009) documented Dscam-mediated trans-synaptic interactions acting through α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid (AMPA) receptors. For clustering of AMPA receptors, during *de novo* synapse formation, a presynaptic input is required. Li et al. (2009) abolished both synaptic transmission and AMPA-like receptor clustering, by blockade of pre- and postsynaptic Dscam. At the same time NMDA-like receptor clustering was found to be Dscam independent (Li et al. 2009). Dscam not only stabilizes presynaptic structures at postsynaptic sites but is required for precise wiring during synapse formation in the learning process (Li et al. 2009). Revitalization of Dscam-mediated signaling by induction of long-term facilitation (LTF) is needed during learning-related synapse formation (Li et al. 2009). LTF induced by a series of 5-HT pulses was shown as an increase in NMDA and AMPA receptors at the *Aplysia* sensory-motor neuron synapse, 12 h *post factum* and was Dscam-dependent (Li et al. 2009). The following processes were Dscam-dependent: remodeling of AMPA receptors, stabilization and formation of new synaptic connections (Li et al. 2009).

The influence of NMDA on DSCAM expression has been confirmed in mouse studies. Incubation of wild-type hippocampal neurons with NMDA resulted in increased locally translated dendritic DSCAM protein levels (Alves-Sampaio et al. 2010). This effect is absent in Ts1Cje hippocampal neurons, where basally increased DSCAM levels are observed (Alves-Sampaio et al. 2010). Moreover, elevation of DSCAM protein level in both wild-type and Ts1Cje hippocampal neurons was abolished by treatment with an NMDA antagonist (APV) (Alves-Sampaio et al. 2010). In turn, DSCAM-mediated mechanisms may be important factors during changes in synaptic plasticity, where earlier history of synapse activity is an important factor.

The contribution of NMDA receptors to neuropsychiatric disorders is well-known. Ketamine, an NMDA antagonist, is capable of producing rapid antidepressant effects in humans (Banasr et al. 2011). Ketamine also produces rapid therapeutic effects for bipolar depression and patients with suicidal ideation (Banasr et al. 2011, Grady et al. 2017) and this is particularly relevant because Amano et al. (2008) demonstrated increased DSCAM levels in bipolar patients. While a possible connection between DSCAM and bipolar disorder was suggested in this study, because of its ethnic undertone further studies are needed to validate the findings. The therapeutic target of ketamine is known, being the mammalian target of rapamycin (mTOR) (Banasr et al. 2011). Postmortem studies of depressed patients found a potential association between mTOR signaling activity and deficits in synaptic proteins (Jernigan et al. 2011). The fast antidepressant-like effect of ketamine was displayed with increased hippocampal and prefrontal cortical mTOR and brain-derived neurotrophic factor (BDNF) levels (Zhou et al. 2013). The increased synthesis of BDNF was proposed as a mechanism to block the NMDA receptor (Szewczyk et al. 2012). Furthermore, chronic antidepressant treatment resulted in increased BDNF levels (Duric and Duman 2013).

Viewed in the context of learning and memory formation, (Banasr et al. 2011, Hoeffer and Klann 2010) the dendritic presence of mTOR signaling elements is very important (Jernigan et al. 2011). The hyperactivation of the Akt-mTOR pathway is a characteristic outcome of DS disability (Troca-Marín et al. 2012). The Ts1Cje model of

DS manifested increased phosphorylation of Akt-mTOR as a result of increased levels of pro-BDNF and BDNF (Troca-Marín et al. 2012). It is known that DS individuals exhibit an age-related increase in BDNF levels (Dogliotti et al. 2010). Studies on mouse DS models suggest that impaired hippocampal synaptic plasticity coupled with impaired local translation is an outcome of basally saturated NMDA signaling, and loss of synaptic sensitivity as a result of changes in Glutamate/BDNF (Troca-Marín et al. 2012). One of the steps in this direction is increased local translation of dendritic mRNA e.g. Dscam (Alves-Sampaio et al. 2010, Troca-Marín et al. 2012).

Based on *Aplysia* research, Li et al. (2011) proposed Dscam-ran trans-synaptic signaling as necessary for the occurrence of long-term synaptic plasticity (LTP). Furthermore, it is known that during synapse formation locally induced synthesis of new proteins and structural modifications are generated, which are then important factors in the back-modulation of synaptic plasticity (Kossut 2007). According to Belichenko et al. (2004) presynaptic terminals and dendritic spines are enlarged in Ts65Dn mice accompanied by thickening of the post-synaptic density of the CA1 region of the hippocampus (Kurt et al. 2004). Taking these all into consideration, the important factor in DSCAM-ran trans-synaptic signaling, is its ability for binding the cytoplasmic fragment with the PDZ domain binding-site (Hortsch and Umemori 2009). Such interactions between PSD-95/Dscam have been reported in the vertebrate retina (Yamagata and Sanes 2010). If these interactions were universal, it would open a wide range of possibilities for DSCAM-dependent signaling at the level of modulation of glutamate receptors, in addition to, NMDAR and metabotropic glutamate receptors (mGluRs). Fig. 3 depicts the proposed role of DSCAM/Dscam, in the cascade of events during synaptic plasticity changes (including research in *Aplysia*).

Considering the important role of DSCAM in Glu receptor modulation, an important question to ask would be, what role does it play in GABA signaling? GABA-γ-Aminobutyric acid is the main inhibitory neurotransmitter in the human brain (Sibley et al. 2007). GABA is synthesized from L-glutamate by L-glutamic acid decarboxylase (GAD) (Sibley et al. 2007). A shift in balance between Glu and GABA is a well-documented factor in the pathophysiology of many psychiatric diseases (Pilc et al. 2008). GABA acts through three classes of receptors ($GABA_{A,}$ $_{B,}$ and $_{C}$) (Sibley et al. 2007).

$GABA_A$ receptors are present at inhibitory synapses both on dendrites, cell bodies, pre-, post- and extra-synaptically (Sibley et al. 2007). An important but often forgotten fact is that GABA plays an inhibitory function in the adult brain while at the same time being a fast-excitatory neurotransmitter in the immature brain (Obrietan et al. 2002). Furthermore, the existence of a positive feedback loop for GABA/BDNF during early development has been proposed (Obrietan et al. 2002). GABA is regarded as an important factor in cognitive and mood disorders and is proposed as one of the main inhibitory factors in Ts65Dn mouse plasticity (Costa and Grybko 2005). In Ts65Dn mice, there is an increased presence of

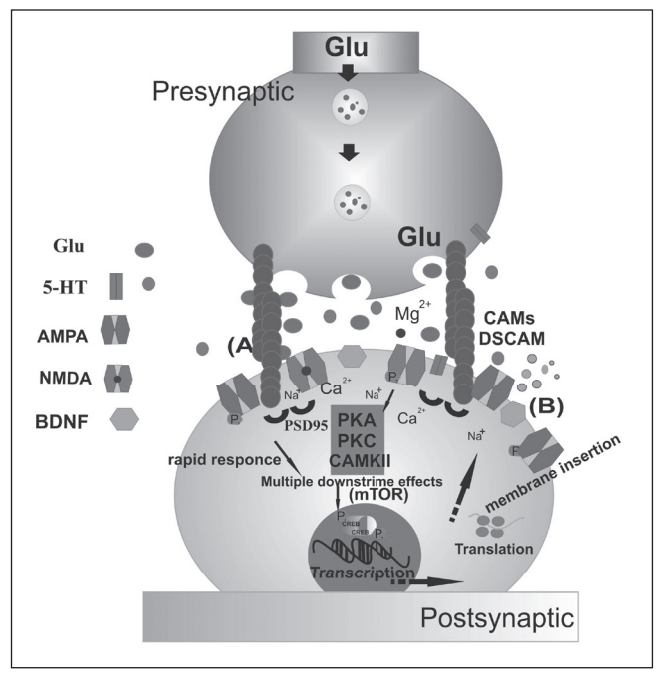


Fig. 3. Schematic drawing of DSCAM localization on a glutamate synapse. Following Li et al. (2009), Dscam is a first-step safeguard in a whole cascade of events during glutamate synapse communication (A). It not only stabilizes the pre-synaptic part to the post-synaptic but is a guarantor of precise timing during this process. When pre-synaptically Glu is released, timed with depolarization, Mg^{2+} ions are released and binding of Glu to the post-synaptic part occurs, allowing permeation of Ca^{2+} ions (Pochwat et al. 2014). NMDA is composed of three main groups of subunits: GluN1, GluN2 (GluN2A, GluN2B, GluN2C, GluN2D) and GluN3 (GluN3A, GluN3B) (Paoletti et al. 2013). It was documented, that during LTP a larger involvement of GluN1/GluN2A in total activity takes part (Paoletti et al. 2013). In opposition, LTD-engages mostly GluN1/GluN2B subunits (Paoletti et al. 2013). Ca^{2+} entry through NMDA receptors, or release by activation of metabotropic receptors, activates intracellular signaling pathways: inositol triphosphate (IP3), activation of CaMKII and insertion of GluR-1 AMPA receptor into the post-synaptic membrane. This process involves Dscam, as Li et al. (2009) documented its role in AMPA receptor stabilization (B). Furthermore, DSCAM protein level is regulated by NMDA-dependent synaptic activity and regulation is lost in trisomic neurons. The whole cascade of events is engaged in signaling, from the synapse to the nucleus, if gene transcription has to occur (mitogen activated protein kinase (MAPK), cAMP-responsive element binding protein (CREB). CREB activation seems to be most important step in this cascade, initiating protein synthesis and leading to occurrence of LTP. One of the early genes in the process of synaptic plasticity is brain-derived neurotrophic factor (BDNF). Increased BDNF release is connected with activation of AMPA and mTOR pathways. These pathways are disrupted in DS persons, as Troca-Marín et al. (2012) showed increased local translation of BDNF, with greatest AMPA receptor delivery and occurrence of an excitatory loop.

GABA-ergic interneurons in the hippocampus and cortex resulting in a GABA-ergic imbalance (Contestabile et al. 2017). Blockade of $GABA_A$ receptors in the hippocampus of these mice may reverse LTP impairment and cognitive efficiency (Cramer and Galdzicki 2012). Immunohistochemical study of the dentate gyrus in Ts65Dn mice showed a shift of GABA-ergic synapses to the spine necks, which may contribute to impairment of synaptic integration (Contestabile et al. 2017).

Glutamate/GABA-ergic imbalance was also suggested as the cause of cognitive behavioral changes in PTSD, DS, depression, and AD (Contestabile et al. 2017, Costa and Grybko 2005, Gao et al. 2014, Li et al. 2016, Pilc et al. 2008). It is now well known that neural cell adhesion molecules (NCAMs) influence GABA-ergic synapse specificity (Sassoè-Pognetto et al. 2011). IgSF9b, a synaptic adhesion molecule is highly expressed in inhibitory synapses of the hippocampus, cortical neurons, and GABA-ergic interneurons. More importantly, it plays a role in major depressive disorder (Shyn et al. 2011, Woo et al. 2013). According to Woo et al. (2013), the down-regulation of IgSF9b may result in high GABA-ergic transmission to pyramidal cells resulting in overall inhibition. However, it is astounding that there is a lack of research on DSCAM and GABA modulation. Table IB summarizes changes observed in the levels of DSCAM, Glu, GABA, and modulation of LTP in the diseases discussed in this review.

CONCLUSIONS

Over the years, research has shown that upregulation of DSCAM is involved in cognitive dysregulation and thus is a major cause of mental retardation. However, to date only a few studies have documented its involvement in mood disorders. Interestingly, DSCAM is regulated by the NMDA pathway and is linked to the dysregulation of m-TOR, resulting in intellectual disability. Although studies of DSCAM in the context of mood are sparse, the association of the Glu pathway with DSCAM indicates a fruitful and exciting track for future research, as this gene/protein seems to be engaged in regulation of dendrite morphology and synaptic plasticity outside of DS.

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