Literature Review
LITERATURE REVIEW

Learning is the process of acquiring knowledge about the world and memory is the process by which that acquired knowledge is encoded, stored and later retrieved (Kandel et al. 2000). Learning and memory are based on modifications of synaptic strength between and among neurons that are simultaneously active. Memory is a highly complex process that involves several brain structures as well as the role of several neurotransmitters. McDonald & White (1993) indicated that different aspects of experience and behaviour are encoded in parallel by many different circuits in the brain. Although there are many neurotransmitter systems in the brain, clinical neuroscience is highly focused on monoamines [DA, NA and 5-HT], ACh and Glu. These neurotransmitters have been linked to cognitive processes such as attention and learning (Winkler et al. 1995; Tang et al. 1999). In recent times, several studies highlighted the importance of plant based drugs, which contribute to modern therapeutics (Das et al. 2002; Hsieh et al. 2006; Kimani & Nyongesa 2008). Number of natural compounds has identified from several plants that could act as nootropic agents (Russo & Borrelli 2005). Substantial work has been carried out to identify the principle compounds enhancing learning and memory (Satyan et al. 1998). A study by Iyer et al. (1998) showed that extract of Lawsonia inermis (Mehendi) leaves possess significant nootropic effect, modulated the level of 5-HT and NA but not DA. Polyherbal formulation BR-16A (Mentat) has been shown to augment acquisition and retention of learning in rats, as well as in states of cognitive deficits (Bhattacharya 1994; Faruqi 1995; Handu & Bhargava 1997). Trasina, a polyherbal formulation, exerts a significant nootropic effect in models of Alzheimer’s disease induced by intra-cerebroventricular
(i.c.v.) injection of colchicine or lesioning by ibotenic acid (Bhattacharya & Kumar 1997).

**Bacopa monniera** Linn., commonly called as Brahmi, has been traditionally used by Ayurvedic medical practitioners in India and was classified as a medhyarasayana, a drug used to improve memory and intellect (medhya) (Russo & Borrelli 2005). *B. monniera* leaf extract contains various active alkaloids such as nicotine, brahmine and herpestine, and triterpenoid saponins such as bacoside A and B (Chatterji et al. 1963, 1965; Kulshreshtha & Rastogi 1973, 1974; Chandel et al. 1977). Later, several other saponin compounds such as bacopaside I, II, III, IV and V were identified (Chakravarty et al. 2001, 2003). *B. monniera* significantly ameliorated the rate of acquisition, consolidation and retention in albino rats during foot-shock motivated brightness discrimination task (Singh & Dhawan 1982). It also attenuated the retrograde amnesia induced by immobilisation induced stress, electroconvulsive shock and scopolamine (Singh & Dhawan 1997). *B. monniera* has a protective effect against phenytoin-induced cognitive deficit in mice during acquisition and retention (Vohora et al. 2000). It also reversed the cognitive deficits induced by colchicine and ibotenic acid as well as reversed the level of ACh (Bhattacharya et al. 2000). Furthermore, *B. monniera* treatment enhances the free radical scavenging enzymes in hippocampus, frontal cortex, and striatum of adult rats suggesting a possible antioxidant effect (Bhattacharya et al. 2000; Chowdhuri et al. 2002), which protect the brain under adverse conditions of stress by modulating the activities of heat-shock protein (HSP70), cytochrome (CYP450) and superoxide dismutase (SOD) (Chowdhuri et al. 2002). The extract having the capacity to scavenge superoxide anion and hydroxyl radical as well as reduced the hydrogen peroxide induced cytotoxicity and
DNA damage (Seiss 1993; Tripathi et al. 1996; Rai et al. 2003). Earlier studies demonstrated an adaptogenic activity, where it reversed acute and chronic stress induced changes (Rai et al. 2003), and anti-convulsive activity (Russo & Borrelli 2005). *B. monniera* induced learning and memory enhancement is attributed to a combination of cholinergic modulation (Das et al. 2002; Kishore & Singh 2005; Holcomb et al. 2006; Dhanasekaran et al. 2007) and antioxidant effects (Singh & Singh 1980; Bhattacharya et al. 2000; Vijayan & Helen 2007). In addition, Sheikh et al. (2007) reported that acute stress induced serotonin level was normalized by pre-treatment with *B. monniera* extract. *B. monniera* reverses the 5-HT$_{2C}$ receptor mediated motor dysfunction in epileptic rats by reducing 5-HT content, 5-HT$_{2C}$ receptor binding and gene expression in hippocampus (Paulose et al. 2008). Diazepam-induced anterograde amnesia in mice (Prabhakar et al. 2008) as well as spatial memory deficit in Alzheimer’s rat model (Uabundit et al. 2010) was also adding support to the earlier reports. It also alter the glutamate receptor binding and NMDA R1 gene expression in epileptic rats (Khan et al. 2008), reducing hypobaric hypoxia induced spatial memory impairment (Hota et al. 2009) and attenuate the N$_{ω}$-nitro-L-arginine (L-NNA) induced amnesia (Saraf et al. 2009). *B. monnieri* and bacoside A treatment prevents the occurrence of seizures in pilocarpine-induced epileptic rats there by reducing the impairment on peripheral nervous system (Mathew et al. 2011). According to Prisila et al. (2011) *B. monniera* extract treatment enhanced the learning ability and retention, by regulating the expression of tryptophan hydroxylase 2 (*Tph2*), 5-HT synthesis and its transporter. Recently, Emmanuvel Rajan et al. (2011) reported that *B. monniera* enhances hippocampus-dependent learning by possibly modulating the 5-HT$_{3A}$ receptor.
Attention and engagement is essential for learning, which is gated by various neuromodulatory mechanisms in the brain. Modulation of neurotransmitters affects different signaling pathways, they are implicated in learning and memory. A strong correlation exists between age-related physiological and psychiatric disorders and brain neurotransmitters concentrations according to several studies, which have reported that brain neurotransmitter levels reduced in association with aging (Brizee 1975; Burchinsky 1985; Santiago et al. 1988; Morgan & May 1990). In the central nervous system neurotransmitters such as DA, 5-HT and NE are involved in basic physiological and behavioural functions (Greengard 2001; Marien et al. 2004). LTP is a leading candidate for the neurophysiological substrate of learning and memory (Brown et al. 1988). LTP can be affected by changes in ACh, DA, NA, and 5-HT systems (Centonze et al. 2001; Munro et al. 2001; Ohashi et al. 2002). The manipulation of cholinergic activity influences cognitive performance (Blokland 1996), and ACh is particularly influential in interaction with 5-HT (Steckler & Sahgal 1995). DA appears to be involved in spatial learning, whereas NE does not seem to be involved (McNamara & Skelton 1993). Among them, 5-HT is considered to be involved in regulation of diverse physiological processes such as sleep-wake cycle, motor activity, feeding, nociception and thermoregulation (Jacobs & Azmitia 1992; Struder & Weicker 2001) and variety of brain functions such as control of mood, aggression, anxiety, pain, learning and memory, and sexual behaviour (Buhot 1997; Mann 1999; Lovingier 1999; Gainetdinov et al. 1999). Study indicated that 5-HT is connected to pathophysiology of disorders including major depression, schizophrenia and obsessive-compulsive disorder (Dutton & Barnes 2008). Memory performance with the systems extracellular 5-HT level analysis revealed that depletion of tryptophan and manipulation of 5-HT receptors
relatively affects memory formation (Schiapparelli et al. 2005, van der Veen et al. 2006).

Impaired or altered 5-HT neurotransmission appears to be a central dysfunction leading to affective states such as depression and anxiety (Kahn et al. 1988a, b; Graeff et al. 1996; Mann 1999), irregular appetite, aggression and pain sensation (Mann 1999) and impairs memory encoding (Khaliq et al. 2006). 5-HT released into the synapse acts on pre- and post-synaptic receptors which mediate different signaling pathway. The cell surface transporters like dopamine transporter (DAT), serotonin transporter (SERT), and the norepinephrine transporter (NET) plays a key role in the reuptake or rapid clearance of the released monoamines into the pre-synaptic nerve terminals (Amara & Kuhar 1993; Torres et al. 2003a, b; Blakely et al. 1994). A study by Quartermain et al. (1988) suggested that monoamine neurotransmitter systems substantially influence memory formation. Monoamine transporters belonging to Na⁺/Cl⁻ dependent transporters determine intensity and duration of signal at synapses (Hersch et al. 1997; Nelson 1998).

Manipulation of monoamine transporters are known to contribute for imbalancing monoaminergic transmission and thereby triggering the pathologic process of several neuropsychological disorders such as depression, bipolar disorder, drug addiction, schizophrenia and stroke (Jayanthi & Ramamoorthy 2005). 5-HT and DA transmission declined during aging because of decreased 5-HT and DA turnover in the striatum and other limbic regions (Meek et al. 1977; Carfagna et al. 1985; Machado et al. 1986; Roubein et al. 1986; Moretti et al. 1987; Venero et al. 1991). Research indicates a combined effect of inefficient phosphorylation and oxidative damage of
TrpH enzyme may be responsible for lower TrpH activity in aging brain. Such alterations in TrpH activity may reduce the level of 5-HT in brain, which may be linked to late-life depression and other brain disorders, such as Alzheimer and Parkinson diseases (Hussain & Mitra 2000). Reduced level of 5-HT and NE and their metabolites was observed in cortex, hippocampus and hypothalamus of aged rats (Birthelmer et al. 2003; Tsunemi et al. 2005).

Despite the fact that duration and intensity of the 5-HT neurotransmission at the synaptic cleft is controlled by the high affinity SERT (Amara & Kuhar 1993) located presynaptically on 5-HT neurons (Blakely et al. 1991; Blakely 2001). Notably, most of the 5-HT neuron cell body was found to be positive for SERT immunoreactivity in the hind brain region (Fujita et al. 1993). SERT plays a vital role within the 5-HT system, limiting 5-HT neurotransmission by removing the neurotransmitter through transport across the presynaptic membrane (Rudnick & Clark 1993; Torres et al. 2003b). Extended to this, SERT knockout model exhibited depressive or despair-like states (Zhao et al. 2006).

5-HT has been shown to involve in regulation of different physiological and mental functions, which act through their diverse receptors located in the CNS (Barnes & Sharp 1999; Hoyer et al. 2002). So far, 15 subtype receptors (5-HT1A, 5-HT1B/1D, 5-HT1E, 5-HT1F, 5-HT2A/2B/2C, 5-HT3A/3B/3C, 5-HT4A/4B, 5-HT5A/5B, 5-HT6, and 5-HT7) were identified and their specific role not yet investigated in detail (Raymond et al. 2001; Hoyer et al. 2002). They belong to the G-protein coupled receptor (GPCR), with the exception of the 5-HT3, which is a ligand-gated ion channel (Macdonald & Olsen 1994; Karlin 2002; Reeves & Lummis 2002; Lester et al. 2004). 5-HT system includes...
receptors (5-HT$_1$, 5-HT$_4$, 5-HT$_5$, 5-HT$_6$, 5-HT$_7$) that inhibit or stimulate adenylate cyclase and (5-HT$_2$) receptor stimulates phospholipase C (Hoyer et al. 1994; Barnes & Sharp 1999; Hoyer et al. 2002). In addition, 5-HT is known to interact with other neurotransmitter systems, through their receptors particularly with cholinergic (Buhot et al. 2000; Meneses 2002; 2003) and dopaminergic systems (Buhot et al. 2000). Age-related decline in post-synaptic 5-HT receptors has been demonstrated in vivo and assumed to be related to changes in psychological functions in the normal aging (Yamamoto et al. 2002). Behavioural study coupled with central or systemic administration of drugs to activate or inactivate specific 5-HT receptors enable to understand the relationship of specific receptor to the defined cognitive functions (Meneses 2003).

The activation of 5-HT$_{1A}$ receptor has been shown to impair performance in a delayed conditional discrimination task (Herremans et al. 1995). The post-synaptic 5-HT$_{1A}$ receptor has been reported to be involved in the consolidation of memory for inhibitory avoidance in rats (Mello e Souza et al. 2001) and its blockade resulted in efficient retention of spatial working memory and non-spatial reference memory by facilitating the ACh release (Millan et al. 2004). Mice lacking 5-HT$_{1A}$ receptor exhibit impaired hippocampal-dependent spatial learning and other functional abnormalities (Sarnyai et al. 2000). 5-HT$_{1A}$ receptor stimulation impaired retention performance in passive avoidance (PA) learning task (Misane & Ogren 2000; Meneses 2003). The activation of 5-HT$_{1B}$ receptor through specific agonist CP 93129 preferentially reference memory (Buhot et al. 1995). These opposite results underline the numerous functional properties of the two receptors, in particular their specific cellular and subcellular locations in the hippocampus (Consolo et al. 1996). A study reported the
effects of 5-HT$_{2A/2C}$ agonist and antagonist on associative learning or conditioned avoidance response (Harvey 1996), which can be manipulated further to develop as therapeutic tools in the treatment of certain memory deficits. The 5-HT$_{2A}$ receptor plays a significant role in both psychotic and cognitive symptoms of illness indicating its importance as a therapeutic target for schizophrenia (Roth et al. 2004; Terry et al. 2004). MDL 100907, a selective 5-HT$_{2A}$ antagonist attenuated the cognitive effect induced by NMDA receptor antagonist (MK-801) (Carlsson et al. 1999), and has shown to interact with PSD-95, which is involved in anchoring NMDA receptor (Xia et al. 2003).

5-HT$_{3}$ heteroreceptor modulated the activity of several neurotransmitters, including cholinergic and glutaminergic system (Ramirez et al. 1996; Aghajanian et al. 1990). The 5-HT$_{3}$ receptor antagonists have been shown to induce learning and memory improvement or to reverse the effect of anticholinergic ligand or age-induced memory loss in rodents and primates (Barnes et al. 1990). Compared to phenylbiguanide/2-methyl-5-HT, 1-(m-chlorophenyl)-biguanide (mCPBG) agonist is selective and more active (Hoyer et al. 1994). Preclinical studies reported that mCPBG impaired consolidation of learning, whereas tropisetron and ondansetron improved performance, and reversed the effect induced by mCPBG (Meneses & Hong 1997; Meneses 1998). Overexpression of 5-HT$_{3}$ receptor in mouse forebrain resulted in enhanced hippocampal-dependent learning and attention (Harrell & Allan 2003). Expression of 5-HT$_{4}$ receptor in the limbic system emphasized their role in different mental function (Lai et al. 2005; Pritchard et al. 2007). Induction of 5-HT$_{4}$ receptor may increase the release of ACh in the frontal cortex (Eglen et al. 1995) and the extracellular level of 5-HT in the hippocampus (Ge et al. 1996). Supporting to that
5-HT₄ receptor agonist (RS67333) enhanced acquisition and consolidation of spatial memory (Orsetti et al. 2003) as well as reduced the memory deficits induced by atropine, scopolamine and 5-HT₄ antagonists (Bockaert et al. 2004). Similarly, the selective 5-HT₆ antagonist (Ro 04-6790) induced strengthening of ACh neurotransmission and an improvement of spatial memory (Rogers & Hagan 2001). The repeated administration of selective 5-HT₆ receptor antagonist (SB-399885) fully reversed the scopolamine-induced deficits in novel object recognition as well as spatial learning in aged rats (Hirst et al. 2006). Different neurochemical studies indicated that 5-HT₆ receptor antagonists enhanced memory consolidation involving DA, Glu and ACh neurotransmission (Dawson et al. 2001; 2003; Reimer et al. 2003). The 5-HT₇ receptor is said to be involved in modulating learning and memory (Cifariello et al. 2008). 5-HT₇ receptor knockout mice showed impairment in contextual fear conditioning (hippocampus-dependent task) and exhibits decreased long-term synaptic plasticity within the CA1 region of the hippocampus (Roberts et al. 2004). Other electrophysiological studies indicated that 5-HT₇ receptor activation modulated the excitability and intracellular signaling of pyramidal neurons in the CA1 region of the hippocampus (Tokarski et al. 2003).

Earlier study indicating that learning evoked changes are accompanied by alterations in gene expression, this also influenced by neurotransmitters, and their receptors and growth factors (Roberson et al. 1999). Manipulations with protein and RNA synthesis inhibitors suggested that experience-dependent alterations in gene expression within neurons may be required for the formation of LTM (Glassman 1969; Barondes 1970; Davis & Squire 1984). An early step in such inducible neuronal gene expression is the activation of constitutively expressed regulatory transcription factors,
such as CREB and its phosphorylation mediated by activated kinases (Montminy et al. 1990; Sheng et al. 1990; Armstrong & Montminy 1993; Arias et al. 1994; Vallejo & Habener 1994; Ghosh & Greenberg 1995; Deisseroth et al. 1996). Subsequent studies found that CREB acts as a universal modulator in memory formation which involved in synaptic activity dependent formation of LTM (Dash et al. 1990; Bourtchuladze et al. 1994; Yin et al. 1994; Bartsch et al. 1998; Yin et al. 1995; Balschun et al. 2003). CREB is an activity-dependent transcription factor that is activated by phosphorylation at Ser$^{133}$ by the cAMP/PKA signalling, growth factor signalling, a Ca$^{2+}$/calmodulin-dependent, and a MAP kinase regulated pathway (Lonze & Ginty 2002), phosphorylated CREB promotes the transcription of target genes (Mayr & Montminy 2001; Lonze & Ginty 2002). Much work has focused on the role of CREB in memory storage and synaptic plasticity (Silva et al. 1998).

Synaptic neurotransmission is regulated by all vesicle trafficking events, such as function of SVs, exocytotic proteins and VDCCs localized to active zones of the pre-synaptic (Augustine 2001; Atwood & Karunanithi 2002). Development of mature synaptic structures requires continuous interaction between the pre-synaptic and post-synaptic neuron (Zoran et al. 1991; Dan & Poo 1994). Formation and stabilization of heterogeneous pre-synaptic structures at the active zone requires contact with an appropriate post-synaptic target (Dan & Poo 1994; Daly & Ziff 1997). Number of vesicle proteins and membrane proteins, such as VDCCs (Ahmari et al. 2000), SV bound proteins including SYT (Littleton et al. 1995; Daly & Ziff 1997), VAMP, synaptobrevin (Ahmari et al. 2000), synapsin (Daly & Ziff 1997) and SYP (Fletcher et al. 1991), soluble N-ethylmaleimide sensitive fusion attachment receptor (SNARE) proteins such as syntaxin and synaptosomal associated protein (SNAP) (Littleton et al.
1995) are found to actively involved in the process. The release of neurotransmitters by calcium triggered synaptic vesicle exocytosis is a key event in interneuronal communication. During exocytosis synaptic vesicles first docks at pre-synaptic membrane called active zones and then undergo priming reactions which leave them in a release-ready state (Sudhof 2004). The release of neurotransmitters is triggered when an action potential causes opening of calcium channels, and controlled by complex intracellular membrane protein (Lin & Scheller 2000; Jahn 2003; Sudhof 2004; Brunger 2005).

Membrane proteins syntaxin 1 and SNAP-25, and the synaptic vesicle protein synaptobrevin 2 are members of the SNARE family, which are believed to be involved in membrane fusion. In aged rats, the ability to sustain LTP is impaired, glutamate release was found to be decreased accompanied with a reduction in the synthesis of SYP (McGahon et al. 1997). Antonova et al. (2001) have shown that potentiation in cultured hippocampal neurons is accompanied by a rapid and long-lasting increase in the number of clusters of pre-synaptic protein SYP. Potentiation involves rapid co-ordinated changes in the distribution of proteins in the pre-synaptic neuron as well as the post-synaptic neuron. SYP immunoreactivity increased in the thalamus of rats after motor training, which possibly correlated with an increased synaptic plasticity (Ding et al. 2002). Similarly, Ishibashi (2002) reported that repeated whisker stimulation in rats induced expression of SYP mRNA in contralateral barrel cortex, suggesting that SYP is involved in modulation of synaptic plasticity. SYP is associated with plasticity related changes in hippocampus (Holahan et al. 2006; Sun et al. 2007), as well as in age-associated impairment (Smith et al. 2000; King & Arendash 2002).
SYT form a large family of C2 domain containing proteins with seven members in *Drosophila* and 19 members in mammals (Adolfsen & Littleton 2001; Craxton 2001). SYT1 is the most abundant Ca\(^{2+}\) binding protein present on synaptic vesicles and accounts for 7% of total vesicle protein (Perin et al. 1990; Chapman & Jahn 1994). SYT is characterized by a pair of calcium binding motifs the cytosolic C2 domains, homologous to those originally described in protein kinase C (Nishizuka 1988). Calcium binds with SYT and phospholipids (Davletov & Sudhof 1993) and interacts with a variety of other presynaptic molecules. Biochemical studies have demonstrated that calcium dependent interactions with SYT suggesting that it may couple calcium influx to vesicle fusion. SYT also binds phospholipids in a calcium dependent manner through lipid interactions with both C2 domains (Brose et al. 1992; Chapman & Jahn 1994; Davis et al. 1999; Earles et al. 2001; Fernandez et al. 2001). Knockout mice lacking SYT have greatly reduced synchronous transmitter release following neuronal stimulation (Geppert et al. 1994). Knock in mice with a mutated SYT that has a 2-fold reduction in calcium dependent phospholipid binding by the C2A domain and displays 50% reduction in evoked release (Fernandez-Chacon et al. 2001). According to Wu et al. (2008) aging is associated with a significant decline in the level of SYT expression in hippocampus, which impaired their spatial memory task.

CaMKII is one of the most abundant proteins in neurons comprising 1-2% and it is an oligomeric, multifunctional serine/threonine kinase. It is expressed pre-synaptically and post-synaptically, but its expression is particularly high in the PSD, where it is ideally located to respond to changes in calcium concentration. There are more than 30 isoforms of CaMKII and numerous substrates, many of which are located in the PSD (Fink & Meyer 2002). CaMKII appears likely to be a mediator of
primary importance in linking transient calcium signals to neuronal plasticity. Activation of CaMKII occurs as a result of autophosphorylation at Thr$^{286}$, and it has recently been shown that if CaMKII is mutated the autophosphorylation is prevented (Giese et al. 1998). Moreover, the activation of CaMKII results in autophosphorylation leading to persistent autonomous activity of the enzyme. Activated CaMKII translocates to PSD (Shen & Meyer 1999), where it is assumed to exert its action by driving the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type of glutamate receptors to synapse (Hayashi et al. 2000). Phosphorylation of AMPA receptor subunits (Barria et al. 1997) causes an increase in current flux through the receptor channel and this leads to enhancement of synaptic response (Derkach et al. 1999). The requirement of CaMKII in induction phase of LTP was confirmed by pharmacological inactivation of CaMKII (Malinow et al. 1989) and the transgenic elimination of its subunit (Silva et al. 1992; Stevens et al. 1994). Consequently, induction of LTP increases the level of CaMKII mRNA (Thomas et al. 1994) and protein (Ouyang et al. 1999). The level of CaMKII autophosphorylation (Fukunaga et al. 1995; Ouyang et al. 1997) and activity (Fukunaga et al. 1993) is also increased after LTP induction by phosphorylating many PSD proteins in both the presence and absence of calcium. Potential substrates are various glutamate receptors, synaptic GTPase activating protein (SynGAP), and post-synaptic density protein-95 (PSD-95) and synapse associated protein-97 (SAP-97). The level of CaMKII in the PSD can affect LTP and hippocampal dependent learning (Yamauchi 2005). Consequently, an alteration in αCaMKII activity in hippocampus is correlated with age-related cognitive deterioration, deficient synaptic plasticity and spatial learning (Giese et al. 1998; Ahmed & Frey, 2005; Zhang et al. 2009).
PSD-95 is one of the most abundant proteins found in the PSD of excitatory synapses (Beique & Andrade 2003). PSD-95, which contains multiple protein-protein interaction domains, has been implicated in memory formation (Migaud et al. 1998). PSD-95, also known as synapse-associated protein-90 (SAP-90), is initially identified based on its abundance in the isolated PSD (Cho et al. 1992; Kistner et al. 1993). PSD-95 is composed of five protein interaction domains: three PSD-95/Dlg/ZO-1 (PDZ) domains, a Src homology 3 (SH3) domain and a guanylate kinase (GK) domain (Sheng & Pak 2000). It directly interacts with NMDA receptor subunits and is reported to be important in NMDA-receptor clustering (Kornau et al. 1995; Neithammer et al. 1996). Suppression of PSD-95 expression attenuated excitotoxicity produced via NMDA receptor activity in brain neurons (Sattler et al. 1999) as well as PSD-95 enhanced NMDAR clustering at synapses (Kim et al. 1996). Aging is accompanied by a decline in the PSD proteins which leads to impairment in organizing signaling complexes interactions with ion channels, membrane receptors, cytoskeletal components at the PSD (Garner et al. 2000; Nicholson et al. 2004). Thus, PSD-95 protein plays a decisive role in controlling synaptic strength and activity dependent synaptic plasticity.