Signalled roads to memory and its degeneration

Priyanka Bhat,¹ Minmoy Chakrabarty,² Vijay Thawani,² Alok Saxena³

¹Department of Pharmacology, Dr. R.P. Government Medical College, Tanda, Kangra, Himachal Pradesh. 176001, ²Department Of Pharmacology, ³Department of Anatomy, Veer Chandra Singh Garhwal Govt. Medical Science and Research Institute, Srinagar, Srikot – 246174, Garhwal, Uttarakhand, INDIA

ABSTRACT

Brain is concerned with the thoughts, feelings, perception, learning, memory and behaviour. The present review discusses some of the prominent molecular pathways governing memory acquisition, storage and subsequent consolidation.

KEYWORDS: Memory, Cell signalling

Introduction

Learning and memory are closely related and are often used interchangeably. It is one of the most fundamental processes of brain that differentiates man from animals, places man in a higher cognitive echelon and therefore, has been a highly sought after domain of research amongst the neuroscientists.

Memory in its broadest sense is explained as "a changed response to a repeated stimulus." This definition also fits reasonably with other non neurological systems like bacteria and immune system.¹ Long term memory is categorised into two main types viz. declarative and procedural memory. Declarative memory, a subset of explicit memory, is the memory of facts and events that are explicitly stored and could be consciously recalled. It is further subclassified into episodic (memory of autobiographical events e.g. times, places, associated emotions, other contextual knowledge)² and semantic memory (memory of meanings, understandings, conceptual knowledge not related to any specific experiences).³

Procedural memory ("knowing what") on the other hand, is the memory of skills e.g., use of objects or movements of the body. It is also known as implicit memory since performance of any task is carried out based on one’s previous experiences.⁴,⁵

Below we discuss the mechanisms of memory acquisition, storage and subsequent consolidation. We also focus on how these mechanisms may result in the deterioration of learning and memory in neurodegenerative disorders.

Notch Signalling

As this exists in almost all multicellular organisms except plants,⁶,⁷ notch signalling plays a crucial role in cell-cell communication (lateral inhibition etc) particularly at the time of differentiation. Before emergence of mice and human paradigms, Drosophila, C. elegans, X. laevis for several decades served as efficient models for exploring the role of notch in various research disciplines like haematopoetic system regulation, cancer research, stem cell research, and age related disorders. After first being cloned in 1985, notch turned out to be an integral membrane protein having a locus in the neurogenic genes.⁸

Notch receptor is a single transmembrane unit encoded by the notch gene. The receptor exists as a heterodimer embedded in the cellular membrane but needs to be cleaved (the process takes place in the Golgi apparatus) before it is incorporated into the membrane as it is synthesised as a single protein.⁹ Subtypes 1 to 4 exist with Notch 1-3 having overlapping expression profiles in developing nervous system.¹⁰ The human homologue of Notch 1 was initially termed as translation associated notch homologue 1(TAN 1).¹¹ The receptor interacts with the ligands on adjacent cells. These ligands encompass Delta like ligand (Dll 1, 3 and 4) and Serrate like ligands which are Jagged 1 and 2. In their extracellular region these ligands carry an epidermal growth factor motif binding domain (EBD) which is necessary for binding of the ligands to the notch receptor. On binding of the ligand to the receptor, signalling is set in motion (Figure 1); resulting in a series of proteolytic events which lead to formation of NICD (Notch intracellular domain). This mobile NICD migrates to nucleus and binds to transcriptional regulator CSL (CBF-1/ RBP-J/ Su-H/ lag-1). The co-repressors are unengaged and co-activators (mastermind - Mam, mastermind like - Maml) recruited causing expression of HES (hairy and enhancer of split) and HERP (hes-related repressor protein) gene families.¹²,¹³

Hes and HERP gene products themselves are transcription factors implicated in neurogenesis and gliogenesis.¹⁴,¹⁵ Further pathway proceeds towards lateral inhibition commencing neural differentiation from an uncommitted progenitor or in an inductive fashion resulting in glial cell formation from committed neurogenic precursor expressing delta ligand;¹² by virtue of which notch regulates neurite growth as well as dendritic arborisation in cortical neurons.¹⁶ This notch dependant dendritic arborisation lays a foundation for memory consolidation or long term potentiation of memory (LTM). NFKB is known to be responsible for memory consolidation/reconsolidation in mice.¹⁷ DNA binding activity of which is affected by Notch 1 in differentiated neurons.¹⁸ Notch concerting with CREB (CAMP Responsive Element Binding Protein) and interplay of NF-κB and CREB are implicated in neuronal plasticity.¹⁹,²⁰ Presenilin facilitates Notch 1 signalling pathway and PS1 dependent gamma-secretase activity is believed to process amyloid precursor protein (APP) and Notch in similar fashion. This, along with evidence of morphological similarities between PS1 deficient and Notch 1 knock-out mice incriminates notch in Alzheimer’s pathophysiology.¹⁷ It would be particularly advantageous to find members of the presenilin/g-secretase complex that principally modulate either the APP or the Notch cleavage which in turn would offer the prospect of more specificity toward beta-amyloid inhibition, with less probability of side effects arising from down-regulating Notch signalling.¹⁸
Sonic Hedge Hog
As neurons lack the property of cell division, ergo axonal along with dendritic arborisation ends up becoming an important determinant in memory processes. Sonic hedgehog (Shh) pathway which gets its name from a video game character, is known to be involved in aforementioned processes. Shh belongs to the family of 3 hedge hogs, a family of protein ligands regulating developmental differentiation during embryogenesis and cellular proliferation. Other two members are Desert hedge hog (Dhh) and Indian hedge hog (Ihh). Initially identified in Drosophila and then named after its mutant phenotype, hedgehog signalling pathway has come a long way over the past few decades.

The canonical Shh signalling pathway (Figure 1) comprises of two transmembrane proteins. Patched (Ptc) a twelve transmembrane unit acts by inhibiting the 7 unit transmembrane protein Smoothed (Smo). Ptc binds to Shh ligand and regulates the activity of Smo which is GPCR like membrane protein acting as a signal transducer, although the dynamics of Ptc and Smo communication still remain unidentified. At rest Smo primarily exists intracellularly and translocates to membrane (on phosphorylation) in response to internalization and degradation of Ptc on contact with Shh. A cascade is then triggered thereby leading to entry of transcription factors Ci/Gli into the nucleus eventually modulating expression of set of genes in a contextual manner for e.g. one of the transcriptional targets being Ptc1 itself.

Mammals express both Ptc1 and Ptc2 both bearing a resemblance in Shh binding affinity. Gli family of transcriptional activators includes Gli1, Gli2, Gli3 which are inhibited by GSK-3 (glycogen synthase kinase 3) and cAMP mediated PKA (protein kinase A). Repression of Shh signalling is mediated by direct interaction of SuFu (Suppressor of Fused) with Gli proteins while a distinct pathway is adopted by DyRK1 (dual specificity Yak1 kinase) for facilitating Gli1 activation of transcription. These all factors provide assorted interventional zones for the treatment of cancers and neurodegenerative anomalies. As far as nervous system is involved Shh signalling modulation is known to have prominent effects in neural development, medulloblastoma pathology and peripheral neuropathies and neuroprotective effects, especially during recovery from stroke. Hippocampal neurones express Ptc and Smo especially in their dendrites, spines and post-synaptic terminals suggesting a role in dendritic arborisation.

Wnt signalling
The wingless-type murine-mammary-tumour virus integration site (Wnt) proteins are a major class of secreted morphogenetic ligands of profound importance in establishing the pattern of development in mammals. The Wnt proteins form a group of secreted palmitoylated signaling proteins of 350-400 amino acids in length. These proteins activate various pathways in the cell. Wnt signalling (Figure 1) involves family members which are secreted glycoproteins and bind to cell surface receptors e.g. Frizzled and upon interaction with many different signalling pathways, effectuate gene expression which is of significance in developmental processes e.g. modulation of organization of body plan during early stages of development and organogenesis at later developmental stages. In mammalian central nervous system (CNS), Wnt signalling is involved in neural induction and patterning in early stages of organogenesis. Among 19 mammalian genes cloned for Wnt, 10 membrane receptors and a myriad of cofactors and regulators, the most comprehensively understood mechanism for Wnt signal transduction is the β-catenin pathway.

The Wnt-ligand binds to Frizzled receptors, kicking off a cascade resulting in displacement of the multifunctional kinase GSK-3β (glycogen synthase kinase 3 beta) from the APC/Axin/GSK-3β-complex. In the absence of Wnt-signal (Off-state), β-catenin, an integral cell-cell adhesion adaptor protein and transcriptional co-regulator, is targeted for degradation by the APC/Axin/GSK-3β-complex. Appropriate phosphorylation of β-catenin by coordinated action of CK1 and GSK-3β leads to its ubiquitination and proteasomal degradation through the TrCP/SKP complex. In the presence of Wnt binding (On-state), Dishevelled (Dvl) is activated by phosphorylation and poly-ubiquitination, which in turn recruits GSK-3β away from the degradation complex. This allows for stabilization of β-catenin levels, Rac1-dependent nuclear translocation and recruitment to the LEF/TCF DNA-binding factors where it acts as an activator for transcription by displacement of Groucho-HDAC co-repressors. Additionally, in complex with the homeodomain factor Prop1, β-catenin has also been shown to

Fig. 1: Pathways in Neuron. DII-Delta like Ligand; Jag-Jagged; NR-Notch receptor; NICD-Notch Intracellular Domain; CSL-CBF-1/ RBP-J/ Su-H/ lag-1; HES-Hairy & Enhancer of Split; HERP-Hes Related Repressor; Shh-Sonic Hedgehog; Ptc-Patched receptor; Smo-Smoothed receptor; Ci-Cubitus interruptus; Wnt-Wingless integration; Fz-Frizzled receptor; Dvl-Disheveled; GSK3-Glycogen Synthase Kinase 3.
act in context dependent activation as well as repression complexes. Importantly GSK-3β is involved in glycogen metabolism and other key pathways, which has made its inhibition relevant to neurodegenerative disorders.28

In vitro data supports the role of Wnt/β-catenin pathway in synaptic plasticity. In the amygdala during fear memory formation, in situ hybridization and RT PCR have revealed many Wnt-signalling genes to be dynamically regulated, with an immediate decrease, followed by an eventual normalization during memory consolidation which suggest that dynamic modulation of Wnt/β-catenin signaling during consolidation is pivotal for the structural basis of long term memory formation.29 Wnt transmembrane signalling pathway in the adult plays a significant role, in postsynaptic dendritic spine morphogenesis and presynaptic terminal neurotransmitter release.20 Wnt has been found to be involved in spatial navigational learning. Water maze experiments have revealed selective elevation of the levels in hippocampus of Wnt7 and Wnt5a, but not the Wnt3 isoform, indicating behavioural selectivity and isoform specificity in Wnt signalling. Wnt7 elevation was found in granule cells with no detectable change in CA3 neurons. Wnt7 elevation was not observed during training, but seven days and 30 days later. It is now thought that Wnt signalling pathways regulate long term information storage in a behavioural, cellular, and isoform specific manner.31 Hippocampal synapses abound in Wnt signalling proteins and cause release of Wnt 3α which in turn, activates Wntβ-catenin signalling and leads to augmentation of long term potentiation (LTP).32 Wnt regulated overactivity of GSK3 which is also potent inhibitor of Gli transcriptional factors of Shh signalling pathway, plays an important role in Alzheimer’s disease progression. This is accounted for GSK3 mediated tau-hyperphosphorylation, increased Aβ production, and microglia mediated inflammatory responses at the vicinity of plaque ultimately manifesting as memory deficits.33

Nogo signalling

A group of evolutionarily conserved membrane proteins, Retinoic (RTNs) are coded by four different paralogs RTN 1 to 4. There are a number of proteins under RTN family but one of them which has gained particular prominence and detailed investigations is RTN 4 or Nogo. Alternative splicing and differential promoter usage of the single gene leads to three subtypes of Nogo protein products namely Nogo A, B, C. They have been found to be one of the most potent neurite growth inhibitors in CNS and are being implicated as the principal molecules which abate axonal regeneration following CNS injuries.34 It is expressed in oligodendrocytes and is known to negatively regulate neuronal growth, leading to increased stabilization of neuronal arborisation but at the cost of extensive plastic rearrangements and regeneration post CNS injuries.35,36 The Nogo A, an inhibitory protein expressed in oligodendrocytes binds to glycosphosphatidylinositol like receptor which is recognised by Nogo 66 (a 66 amino acid fragment). Nogo receptor (NgR) also has other ligands oligodendrocytes myelin glycoprotein (OMgp) and myelin associated glycoprotein (MAG - a transmembrane protein of the Ig superfamily) but absence of cytoplasmic domain of the receptor implies involvement of other molecules in the signalling pathway (Figure 2). Crosstalk between NgR and p75 (a low affinity neurotrophin receptor), interaction being through extracellular domains is known to affect axonal growth. This inhibitory effect of MAG and Nogo is resultant of p75 mediated insult, as evidence indicates absence of p75 is related with enhanced axonal growth and density.37 Out of the different proteins that bind to p75 RhoA is of utmost relevance in inhibiting neurite outgrowth hampering axonal lengthening.38 Recently Lingo1, an additional component of NgR receptor complex has been identified. Binding of Nogo/MAG on NgR activates p75 which causes phosphorylation and activation of Rho and subsequent activation of a downstream effector Rho associated Coiled-coil containing protein kinase (ROCK) which is a serine/threonine protein kinase; mediating growth cone collapse and neurite outgrowth inhibition. Isoquinoline derivatives like fusicid, hydrasyljafulisid (a fusicid metabolite), Y-27632 (4-aminopyridine derivative) are ROCK inhibitors being developed for axonal regeneration.39

Conclusion

Developing parts of brain influence decisions in the operation of cells belonging to complex circuits. The cascades discussed are some of the prime molecular dictators which lay down memory. The intertwined pathways are robust and resilient. Nevertheless, they are also delicately balanced and are susceptible to dysregulation by various factors which lead to a collapse of the brilliantly orchestrated flow of information across the grid which grossly manifests as neurodegeneration. The increasing ability to monitor the molecular events and the expertise to tweak them in these circuits ensure that
we will witness a more detailed mapping of the entire landscape of memory and forgetfulness which should, in turn, usher in the moments when we should be able to unmask putative druggable targets to deal with neurodegeneration.

Article complies with International Committee of Medical Journal editor uniform requirements for the manuscripts.

Competing interests – None, Source of Funding – None

Received Date: 28 January 2012

Revised Date: 5 March 2012

Accepted Date: 11 April 2012

References

1. Smith CUM. Elements of Molecular Neurobiology. 3rd ed. West Chichester, West Sussex England: John Wiley & Sons Ltd. 2002; 1–613.
2. Tuilving E. Precis of Elements of Episodic Memory. Behavioural and Brain Sciences 1984; 7(2): 223–238.
3. Squire LR and Zola SM. Episodic memory, Semantic memory and Amnesia. Hippocampus 1998; 8: 205–211.
4. Schacter DL. Implicit memory: history and current status. Journal of Experimental Psychology: Learning, Memory, and Cognition 1987; 13: 501–518.
5. Okano H, Hirano T and Balaban E. Learning and Memory. Proceedings of National Academy of Sciences 2000; 97: 12403–12404.
6. Nichols SA, Dirks W, Pearse JS, et al. Early evolution of animal cell signaling and adhesion genes. Proc Natl Acad Sci USA. 2006; 103: 12451–12456.
7. Wigge PA and Weigel D. Arabidopsis genome: life without notch. Curr Biol. 2001; 11: R112–114.
8. Marsolais AJ. The role of notch signalling in learning and memory. MSc. Thesis, Department of Physiology; University of Toronto; 2009.
9. Joepss L and Hong W. Notch signalling, brain development and human disease. Pediatric Research 2005; 57: 104R–109R.
10. Lardelli M, Dahlstrand J and Lendahl U. The novel Notch homologue mouse Notch 3 lacks specific epidermal growth factor-repeats and is expressed in proliferating neuroepithelium. Mech Dev. 1994; 46: 123–136.
11. Iso T, Kedes L and Hamamori Y. HES and HERP families: multiple effectors of the Notch signalling pathway. J Cell Physiol. 2003; 194: 237–255.
12. Morrison SJ, Perez SE, Qiao Z, et al. Transient notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells. Cell 2000; 101: 499–510.
13. Redmond L, Oh SR, Hicks C, et al. Nuclear Notch1 signaling and the regulation of dendritic development. Nat Neurosci. 2000; 3: 30–40.
14. Boccia M, Freudenthal R, Blake M, et al. Activation of hippocampal nuclear factor-kappa B by retrieval is required for memory consolidation and storage. Proc. Natl Acad Sci USA. 2006; 79: 123–135.
15. Wang Y, Chan SL, Miele L, et al. Involvement of Notch signaling in hippocampal synaptic plasticity. Proc Natl Acad Sci USA. 2004; 101: 9458–9462.
16. Wang H, Hu Y and Tsien ZJ. Molecular and systems mechanisms of memory consolidation and storage. Proc. Natl Acad Sci USA. 2006; 79: 123–135.
17. Morishima-Kawashima M and Ihara Y. Alzheimer’s disease: beta-Amyloid protein and tau. J Neurosci Res. 2002; 70: 392–401.
18. Selkoe D. Presenilin, Notch, and the genesis and treatment of Alzheimer’s disease. PNAS 2001; 98(20): 11039–11041.
19. Tammy D, Justyna TR, Tom C, et al. The Hedgehog Pathway and Neurological Disorders. Annu Rev Neurosci. 2006; 29: 539–63.
20. http://www.rndsystems.com/mini_review_2006/Hedgehog.html
21. Denef N, Neubuser D, Perez L, et al. Hedgehog induces opposite changes in turnover and subcellular localization of patched and smoothened. Cell 2000; 102: 521–531.
22. Carpenter D, Stone DM, Brush J, et al. Characterization of two patched receptors for the vertebrate hedgehog protein family. Proc Natl Acad Sci USA. 1998; 95: 13630–13634.
23. http://www.biocarta.com/pathfiles/h_shh_pathway.asp
24. Ronald SP, Ya-Xian W, Mark PM, et al. Sonic hedgehog distribution within mature hippocampal neurons. Communicative & Integrative Biology 2011; 4(6): 775–777.
25. Cadigan K.M., Nusse R. Wnt signaling: a common theme is animal development. Genes & Development 1997; 11: 3286–3305.
26. Moon RT, Kohn AD, De Ferrari GV, et al. Wnt and beta catenin signalling: diseases and therapies. Nat Rev Genetics. 2004; 5: 691–701.
27. Gordon MD. Wnt signalling: multiple pathways, multiple receptors and multiple transcription factors. J Biol Chem 2006; 281: 22429–22433.
28. De Ferrari, Chacon MA, Barria MI, Garrido JL, Godoy JA, Olivares G, et al. Activation of Wnt signalling rescues neurodegeneration and behavioural impairments induced by beta amyloid fibrils. Molecular Psychiatry 2003; 8: 195–208.
29. Maguschak KA, Ressler KJ. Wnt signalling in amygdale dependent learning and memory. Journal of Neuroscience. 2011; 31: 13057–13067.
30. Inestrosa NC, Arenas E. Emerging role of Wnts in the adult nervous system. Nature Reviews Neuroscience 2010; 11: 77–86.
31. Tabatadze N, Tomas C, Mc Gonigal R, et al. Wnt transmembrane signalling and long term spatial memory. Hippocampus 2011.
32. Jiangong Y, Chang SP, Shao JT. Activity-dependent Synaptic Wnt Release Regulates Hippocampal Long Term Potentiation. 2006; 281: 11910–11916.
33. Claudio H, Richard K, Simon L. The GSK3 hypothesis of Alzheimers disease. Journal of Neurochemistry 2008; 104: 1433–1439.
34. Yan R, Shi Q, Hu X, Zhou X. Reticulon proteins: emerging players in neurodegenerative diseases. Cell Mol Life Sci. 2006; 63: 877–889.
35. Martin E schwab. Functions of Nogo proteins and their receptors in the nervous system. Nature Reviews Neuroscience 2010; 11:799–811.
36. Tatadia G, Fumio N, Timothy V, et al. Identification of the Nogo inhibitor of axon regeneration. Nature 2000; 293: 439–444
37. Walsh G, Krol K, Krutchker K, et al. Enhanced neurotrophin induced axon growth in myelinated portions of CNS in mice lacking p75 neurotrophin receptor. J. Neurosci 1999; 19: 4155–4168.
38. Moses V Chao. Neurotrophins and their receptors: A convergence point for many signalling pathways. Nature Reviews Neuroscience 2003; 4: 299–309.
39. Takekazu K, Atsushi Y, Nobuyoshi I, et al. The therapeutic effects of Rho-ROCK inhibitors on CNS disorders. Therapeutics and Clinical Risk Management 2008; 4: 605–615.