Gene Control of Synaptic Plasticity and Memory Formation: Implications for Diseases and Therapeutic Strategies

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Abstract: There has been nearly a century of interest in the idea that information is stored in the brain as changes in the efficacy of synaptic connections between neurons that are activated during learning. The discovery and detailed report of the phenomenon generally known as long-term potentiation opened a new chapter in the study of synaptic plasticity in the vertebrate brain, and this form of synaptic plasticity has now become the dominant model in the search for the cellular and molecular bases of learning and memory. Accumulating evidence suggests that the rapid activation of the genetic machinery is a key mechanism underlying the enduring modification of neural networks required for the laying down of memory. Here we briefly review these mechanisms and illustrate with a few examples of animal models of neurological disorders how new knowledge about these mechanisms can provide valuable insights into identifying the mechanisms that go awry when memory is deficient, and how, in turn, characterisation of the dysfunctional mechanisms offers prospects to design and evaluate molecular and biobehavioural strategies for therapeutic prevention and rescue.

Key words: LTP, hippocampus, ageing, Alzheimer's disease, Duchenne muscular dystrophy, environmental enrichment, animal models.

INTRODUCTION

It is generally accepted that memory for events are represented in the brain as specific spatio-temporal patterns of synchronised firing activity in dynamically associated assemblies of neurons forming transiently active networks, and that changes take place at the cellular level to store these representations. This is based theoretically on the notion that the mechanisms sub-serving the formation and storage of memory representations reside in activity-driven modifications of synaptic strength and remodelling of neural networks so that the specific distribution of activity can later be restored during retrieval [1,2]. This prevailing view gained coinage nearly 30 years ago with the discovery of an enduring form of activity-dependent synaptic plasticity in the mammalian brain, known as long-term potentiation, or LTP [3]. In their original discovery, Bliss and Lømo showed that brief bursts of high-frequency stimulation to the perforant path, the major cortical input to the hippocampus, induce a robust and long-lasting increase in the efficacy of synaptic transmission at synapses of the target neurons, the granule cells of the dentate gyrus. That which is most remarkable about this form of plasticity is its extremely persistent nature. While it can be induced within fractions of seconds using short bursts of tetanic stimulation, the modification can last for periods of weeks or even months, thus leaving a quasi-permanent trace of past activation of the synapse. Since then, considerable attention has been directed towards determining the cellular and molecular mechanisms that underlie synaptic plasticity and its contribution to memory storage. In this review, we begin with a brief overview of recent advances in some of the key molecular mechanisms that may mediate neuronal plasticity and memory formation, and then describe examples showing how what is known about these mechanisms, although only partially understood, can help exploring memory malfunction in certain clinical disorders. We limit ourselves to three conditions, the compromised memory function often observed with the progression of age, and the more severe memory loss associated with two neurological diseases, Duchenne muscular dystrophy (DMD), an early onset single-gene disease caused by a mutation in the dystrophin gene, and Alzheimer's disease (AD). We also explore what prospects lie ahead in terms of molecular and behavioural rescue strategies that may proved fruitful for compensating for some of the dysfunctional cellular mechanisms responsible for the impaired memory ability. We focus on the hippocampus, a structure of the medial temporal lobe, for human neuropsychological and brain imaging research as well as experimental studies in animals have for years highlighted the contribution of this structure to the formation of explicit, relational and episodic categories of memories; and because cellular and molecular accounts of memory are for a large part

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the most intensively studied in this structure, linking hippocampally-mediated memory storage to synaptic plasticity and its molecular mechanisms.

MOLECULAR MECHANISMS OF SYNAPTIC PLASTICITY AND THE BASES OF MEMORY

Several reviews have presented extensive discussions of the cellular and molecular biological bases of LTP [4-9]. Here, we focus on a few critical steps in these processes. The first is the induction process. The primary mechanism for the induction of LTP at most glutamatergic, modifiable synapses in different cortical and subcortical brain structures, is the activation of a membrane protein assembly, the voltage-gated NMDA subtype of glutamate receptor. At these synapses, whereas normal transmission is primarily mediated by the AMPA-type receptor channel complex, intense synaptic activation that trigger LTP activates the NMDA receptor to produce an influx of calcium into the postsynaptic neuron, initiating the intracellular events that lead to endurable synaptic changes. The activation of certain types of metabotropic glutamate receptors coupled to second messenger systems contributes to the elevation of calcium by mobilising intracellular calcium stores. Receptors such as the NMDA and AMPA receptors possess cytoplasmic domains that serve as molecular platforms for protein assemblies into functional scaffolding complexes, bringing proteins in close proximity for protein-protein interactions. At this step, calcium and second messenger proteins activate several intracellular kinase signalling cascades, including protein kinase C (PKC), calcium/calmodulin-dependent protein kinase II (CaMKII), cAMP-dependent protein kinase A (PKA), and the mitogen-activated protein kinase (MAPK) (e.g., [10-12]). The phosphorylation of these kinases occur within minutes after the initial induction process, and this leads to the activation of selective downstream protein substrates, an essential mechanism for progressively engaging persistent molecular modification of the synapse. These mechanisms are complex however, as there is abundant cross-talk between signalling kinase pathways with both positive and negative interactions [10]. Moreover, they can be differentially regulated by the activity of protein phosphatases [13-15] and each can lead to the activation of diverse downstream protein targets, most of which are as yet unidentified. This suggests high combinatorial interactions in the mechanisms leading to the co-ordinated molecular changes that occur at the synapse.

What the molecular consequences of activation of cell-surface receptors and the resulting transduction cascades are and how they lead to enduring modifications at the synapse, has not yet been fully clarified. The identification of certain protein substrates, however, has highlighted two major routes by which the synapse may be modified. On the one hand, kinase-dependent phosphorylation of receptor subunits and of other proteins lead to an increase in the conductance of receptor and channels and, presynaptically, to a modification of proteins of the exocytotic machinery to increase neurotransmitter release. Another important consequence is a modification of receptor composition at the synapse. One example is the mobilisation of the trafficking pathways for the delivery and insertion of specific AMPA-receptor subunits at the synapse, resulting in an increase in the number of receptors at the synapse and in the conversion of previously silent synapses to active synapses (see [8] for a review). A second road is a kinase-dependent phosphorylation of specific transcription factors leading to nuclear gene transcription and *de novo* synthesis of proteins and their delivery to the activated synapses. This is a key mechanism for the stabilisation of synaptic changes on a long time scale [16-18]. This genomic response of neurons is accomplished via two distinct, but interdependent processes. First, activated transcription factors turn on the expression of regulatory immediate early genes (IEGs), then IEG protein products direct co-ordinated regulation of the expression of a whole host of late-response, effector genes by transcriptional control. A series of investigations have provided evidence for this model. For example, the IEGs *zif268*, *c-fos*, *BDNF*, members of the *jun* family, *Arg3.1* or *Homer*, are activated very rapidly and transiently after the induction of LTP (see [19-21] for reviews) and this is followed by temporally-restricted and overlapping waves of expression of many late-response genes, including genes encoding kinases or glutamate receptor subtypes [22-24]. The mRNA or protein products of some of the IEGs, such as *BDNF*, *Homer,* or *Arg3.1* which may be translated in the dendrites to facilitate synapse-specific modification, have a direct role at the synapse [25, 26], whereas others such as *zif268* encode inducible nuclear transcription factors that bind to specific response elements on the promoter region of late-response genes to trigger their transcription.

To take an example, one of the prominent signal transduction pathway coupling cell-surface receptor activation to the genomic response of neurons is the MAPK cascade (see [27] for review). Recent experiments have shown that this cascade is directly implicated in the transcription of the IEG *zif268* during hippocampal synaptic plasticity [28]. The MAPK cascade is also involved in transcriptional regulation of the IEGs *Arg3.1*, *Homer* and *c-fos* in different systems [26, 29-31]. In LTP, the induction process leads to rapid phosphorylation of MAPK, which then activates indirectly the transcription factor CREB and translocate to the nucleus to phosphorylate the transcription factor Elk-1. Then, in turn, phosphorylated Elk-1 and CREB bind respectively to the SRE and CRE sites on the promoters of several IEGs, including *zif268*, thereby triggering their transcription [28]. Disruption of this

cascade, either by blocking MAPK phosphorylation [32] or by genetic inactivation of *CREB* [33] or of *zif268* in mutant mice [34] prevents the late phases of LTP. Thus, the transient activation of IEG transcription acts as a molecular switching process for engaging the neurons into a full genomic response leading to the enduring reorganisation of the synapses and growth of new synaptic connections.

Each of these steps has been shown to be essential for learning. For example, preventing the induction process by pharmacological blockade of the NMDA receptor or by genetic inactivation of the R1 subunit of the NMDA-receptor in mutant mice, impairs both hippocampal LTP and diverse spatial and non-spatial forms of learning [35-38]. This also results in adverse repercussions on cellular correlates of learning such as hippocampal cells' firing to specific cues in fear conditioning [39] or the fine tuning and positional firing of hippocampal place cells [40, 41]. This suggests that interfering with NMDA receptor-mediated plasticity impairs learning by preventing the formation of reliable and stable neural representations of learned events. Similarly, deletion or mutations in genes encoding kinases such as CaMKII, PKC or PKA, phosphatases, or many other proteins engaged into cell-signalling results, with only a few exceptions [42], in correlated deficits in hippocampal LTP and in types of learning that require the hippocampus [13, 43-48]. Using a complementary strategy, transgenic mice overexpressing the NR2B regulatory subunit of the NMDA receptor [49] or expressing an auto-inhibitory domain of the phosphatase calcineurin [14] have enhanced hippocampal LTP and improved performance in several learning and memory tasks. Thus, together with a number of studies showing similar molecular changes in synapses after LTP and after learning (reviewed in [24]), the available evidence suggest that the neurobiological mechanisms of synaptic plasticity are recruited during, and required for learning.

Several experiments have also provided evidence that the molecular mechanisms underlying the long-term maintenance of synaptic plasticity are required for the expression of long-term memory. For example, inhibition of protein synthesis affects long-term memory without otherwise impairing short-term memory [50] and prevention of LTP decay was shown to retard forgetting of spatial memory [51]. In the mammalian brain, the MAPK-CREB pathway has been shown to be activated and necessary for certain forms of learning [33, 52-58]. Similarly, the expression of IEGs such as *zif268* and *Arg3.1* is increased in neurons of different structures after defined learning tasks [59-63] and inactivation of the *zif268* gene in mutant mice [34] or antisense oligonucleotides against *Arg3.1* [64] shows that these genes are required for the expression of long-term memory. Thus, interfering with the molecular mechanisms underlying the stabilisation of synaptic plasticity corrupts memory storage processes. At this point, it seems a reasonable hypothesis to suggest that activity-driven modifications of synaptic strength and remodelling of neural networks that engage the molecular machinery underlying the expression of LTP are crucial to the storage of memories. Although a basic understanding of the cellular and molecular mechanisms underlying synaptic plasticity and memory formation has only begun to emerge, uncovering of some of these mechanisms will, in turn, provide a strong biological basis for investigating the relations between diseases that affect memory function, the expression of plasticity in neurons and the underlying molecular mechanisms.

IN SEARCH OF CELLULAR AND MOLECULAR DYSFUNCTION ASSOCIATED WITH MEMORY DISORDERS

Ageing

During the course of normal ageing the brain undergoes a number of changes, such as cell death in certain brain regions; shrinkage of neurons and their processes; the development of senile plaques and neurofibrillary tangles; a greater susceptibility to mitochondrial damage; and an increase in brain inflammation and oxidative stress. The overall loss of volume and weight of the brain cannot be accounted for solely by the large scale loss of neurons [65], and modification of neurons and their processes such as atrophying neurons and synapses or dendritic regression may constitute the major cause. In addition, deposits of amyloid plaques and neurofibrillary tangles - two neuropathological hallmarks of Alzheimer's disease (AD) - are a consistent feature of normal ageing but they are considerably less numerous and less widely distributed than in the brains of patients with Alzheimer's disease [66]. In healthy older people these changes may be very modest and result in varying degrees of age-related cognitive decline.

The molecular basis of ageing in the brain has, to date remained relatively unexplored. Many studies have suggested that alterations in the stability of nuclear and mitochondrial genes, the production of reactive oxygen species, neuroendocrine dysfunction, altered calcium metabolism, constitute but a few of the potential targets of brain malfunctioning in ageing. A large scale genomic analysis of the aged brain showed that of the 6347 genes screened, there was a 2.1 fold alteration in the expression of 2% of the genes, either showing an increase or a decrease [67]. Proteomic analysis shows that there is a similar proportion of proteins that are altered during ageing [68]. Of the genes altered in the cortex, 20% are genes that are implicated in inflammatory or immune responses. It is not known, however, whether an increase or a decrease in the expression of genes and the levels of proteins during ageing contributes to a

neurodegenerative process or an adaptive/protective process (see [69]).

One important approach to understand how the memory deficits in aged rats may occur has been to examine synaptic plasticity in the brain of aged rodents and determine whether there are changes in the signalling cascades and molecular mechanisms that underlie the different phases of LTP. Aged rodents have been shown to have deficient LTP, at least in the hippocampus. That which has been shown consistently is a normal induction of LTP with no difference compared with young rodents, however the later phases of LTP are not maintained and synaptic transmission rapidly declines back to pre-induction levels[70-74]. Several studies have shown that there is alteration in NMDA receptor function [75-78]; calcium homeostasis [79]; certain kinase signalling pathways and the regulation of certain genes [80, 81] known to be implicated in synaptic plasticity and learning.

In our own research, we have found that aged rats fall into two subgroups in terms of the maintenance or stabilisation of hippocampal LTP; those in which LTP decays within 3 hours and those in which LTP is maintained as in the young rats [82]. This variability in the capacity for synaptic plasticity in aged rats shows a striking similarity with the variability observed with learning, and suggests that alteration in activity-driven gene transcription in neurons may at least in part be responsible for the dysfunctional plasticity and memory function. We have investigated whether certain genes that are known to play a role in different forms of synaptic plasticity, or have been linked with age-related neuropathology, may be differentially regulated in aged rats. We found this to be the case for several genes. For example, the gene encoding syntaxin 1B, a presynaptic protein involved in exocytosis, is upregulated after LTP and this molecular mechanism has been implicated in transsynaptic plasticity [83, 84], a form of plasticity in which neuronal or synaptic modifications may be propagated through neural circuits [85]. In both aged groups of rats, regardless of whether LTP was sustained or not, there was attenuation of LTP-induced upregulation of the gene compared with young rats. Regulation of the gene encoding αCaMKII, a kinase essential for synaptic modification at the potentiated synapses, was also altered in aged rats. For this kinase, the mRNA is expressed both in the nucleus and in the dendrites. In aged rats, upregulation of the nuclear mRNA was absent whether LTP was maintained or not, while in the dendrites there was an increased expression in aged rats with normal LTP, but not in the aged rats with decremental LTP [82], showing a dysfunction in some of the molecular mechanisms of synaptic plasticity in ageing.

A complementary pattern of findings was observed with the regulation of two different isoforms of the amyloid precursor protein (APP) and of the gene encoding α-synuclein. Although APP expression increases following the induction of LTP [86], the isoform lacking the KPI domain appears to play a more prominent role in synaptic plasticity [87, 88]. In the aged rats, we found that only the isoform of APP lacking the Kunitz protease-inhibitory (KPI) domain was upregulated in the group in which LTP was maintained, as it was with the young rats, but not the total APP in contrast to the young rats. α-synuclein, a protein shown to be associated with senile plaques in several types of neurodegenerative diseases, has also been implicated in apoptosis. In the young and the aged rats in which LTP was maintained, there appeared to be trend towards a downregulation of the gene whereas there was no change in expression in the aged rats with decremental LTP [74]. These results together are consistent with the idea that an alteration in activity-dependent transcriptional regulation in neurons of the ageing brain may in part underlie some of the subtle deficiencies in neuronal plasticity that may give rise to the cognitive deficits often observed in ageing.

Alteration in the regulated expression of several genes during ageing suggests the possibility of dysfunctional upstream signalling by certain transcription factors. Although this has not as yet been examined in detail, recent studies have highlighted a potential implication of nuclear retinoic acid receptors, DNA-binding proteins that regulate the expression of certain effector genes after activation by specific ligands. The expression of retinoid receptors is reduced in the ageing brain compared to the adult level [89] and knockout mice have impaired LTP [90]. Moreover, a recent study showed that administration of the vitamin A metabolite, retinoic acid in aged mice is effective in normalising retinoic acid receptor levels and in ameliorating the age-related deficits in hippocampal LTP and learning [91].

The differential regulation of these genes during ageing shows examples of the type of molecular modifications that underlie some of the subtle changes in the brain during ageing that may give rise to the cognitive deficits observed. As suggested above, to date we do not know whether these changes may be due to neurodegenerative processes, or whether they constitute an adaptive or protective mechanism.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an example of an early onset genetic disease associated with intellectual and learning disabilities, which appears to result from the partial disorganisation of a molecular scaffold of proteins within the submembraneous cytoskeleton network. This fatal and most frequent X-linked form of muscular degeneration is caused by the absence of

dystrophin, a spectrin-like cytoskeletal protein that links a complex of intrinsic membrane proteins to the actin-based cytoskeleton. In common with several myopathies, DMD is associated with alterations of the nervous system and it has long been recognised as a cause of significant cognitive and behavioural disabilities [92]. The cognitive profile of DMD patients is usually characterised by reduced IQ, impairments in learning and memory, selective attention disorders, and language disabilities. The cognitive deficits in DMD are non-progressive; they may occur before the onset of muscular degeneration and cannot be attributed to environmental or secondary factors associated with the patients' physical decline [93, 94]. Although the exact nature of the cognitive deficits still remains debatable, specific deficits in immediate and delayed recall, digit span and auditory comprehension suggest a selective impairment in information processing and working memory [95-97].

The biological substrate of the cognitive impairment in DMD is still largely unknown. Although dendritic abnormalities have been described [98], there is no gross histological abnormalities in the brain of DMD patients [99] and it is currently hypothesised that brain alterations are most likely to be located at the cellular level. Because dystrophin, the protein responsible for DMD, is normally expressed in both muscle and brain, the genesis of the cognitive deficits has been initially linked to the absence of neuronal dystrophin. In normal individuals, the brain-specific isoform of dystrophin is detected at the soma and dendrites of pyramidal cells in brain structures involved in cognitive functions, such as the hippocampus and neocortex. It is enriched in postsynaptic densities (PSDs) [100, 101], specialised regions of the subsynaptic cytoskeletal network that have a critical role in synaptic transmission and plasticity. The physiological importance of dystrophin in neuronal function has been supported by studies in the *mdx* mouse, the first dystrophin-deficient mouse model of DMD [102]. The *mdx* mutants show altered neuronal calcium homeostasis [103], enhanced sensitivity of CA1 hippocampal neurons to hypoxia [104] and impaired memory retention in non-spatial learning tasks [105, 106]. This model also demonstrates altered brain energetic and biochemical homeostasis, which appears to be a common feature in DMD patients (see [107] for a review). These data have placed dystrophin as a candidate protein involved in the genesis of cognitive deficits in DMD. However, several non-muscle C-terminal forms of the full-length dystrophin may play an important role. These include Dp140, expressed mainly in glial cells, and the most abundant protein product of the dystrophin gene, Dp71, associated with synaptic plasma membranes and expressed in brain areas prone to synaptic plasticity, such as the olfactory bulb and dentate gyrus [101, 108]. It is believed, although not demonstrated, that the heterogeneity of the cognitive profile in DMD reflects the variety of gene mutations among DMD patients and that Dp71 and Dp140 are responsible for the most severe impairments in cognitive functions [109, 110].

At the cellular level, dystrophin is a critical component of a multiprotein complex, the dystrophin-associated glycoprotein (DAG) complex, localised to the inner membrane in various cell types and associated with distinct dystrophin-gene products or structural homologues such as utrophin and dystrobrevin (e.g., [111, 112]). This provides a molecular bridge between various proteins of the extracellular matrix, membrane proteins and intracellular signalling molecules. At the neuromuscular junction, the DAG complex participates in the stabilisation of acetylcholine receptors and acetylcholinesterase [113, 114] and the lack of dystrophin results in the collapse of the associated DAG complex, leading to disruption of sarcolemmal membrane integrity and altered calcium homeostasis (see [115] for a review). The function of dystrophin/DAG complexes in the brain is however less known. Different DAG complexes may interact with distinct types of synaptic receptors depending on their cell-specific expression. For example, the selective association with $GABA_A$ receptors at inhibitory synapses [116, 117] suggests that dystrophin/DAG complexes do not solely have a structural role within the PSDs, but also endorse the capacity to participate in the modulatory actions of a large number of cellular signalling pathways. Moreover, multiple interactions between dystrophin and DAGs are modulated *in vitro* by enzymes implicated in synaptic plasticity and learning, such as PKA, PKC, CaMKII, and MAPK (e.g., [118]). In all, this suggest an important role for these complexes in membrane integrity, ion channel physiology, cellular signal integration and structural reorganisation of the synapse (see [119, 120]; for reviews).

The generation of several mouse models of DMD displaying a range of differential expression of dystrophin-gene products [121] yielded the opportunity to correlate specific dystrophin-gene mutations with distinct cognitive deficits. One of these models, the *mdx* mouse, lacks the full-length dystrophin alone. Behavioural studies have confirmed that dystrophin deficiency in *mdx* mice correlates with learning impairments. The mice have impaired memory retention in non spatial tasks [105, 106], but also in delayed spatial alternation [106]. However, spatial learning in the water maze is not impaired in *mdx* mice [122], and both working and reference memory are preserved when the mice are submitted to a spatial discrimination task in a radial maze [123]. This suggests that dystrophin deficiency induces an alteration in selective forms of memory. The detailed behavioural analysis of the *mdx* mice [106, 124] indicates mild but selective learning and memory deficits in this mutant, not associated with obvious motor, emotional or motivational disturbances. The deficits are characterised by slower acquisition of a procedural bar-pressing task,

although the mice can progressively master the task, and by retention impairments at long delays in procedural and recognition memory tasks, suggesting a role for this protein in the consolidation of long-term memories. In all, this provided evidence that dystrophin dysfunction is sufficient to produce specific learning and memory impairments in *mdx* mice, although moderate compared to the profound cognitive deficits and mental retardation observed in the most severely affected DMD patients.

The *mdx*^{3Cv} mutant mouse, which lacks both the full-length dystrophin and the shorter C-terminal products of the dystrophin gene [126], exhibits alterations of emotional processes expressed as enhanced anxiety-related behaviours [124], an aspect of the DMD syndrome that may participate to the increased severity in the cognitive impairment of patients lacking Dp71 [109]. However, they show less of an impairment in spatial [123] or non-spatial learning tasks than the *mdx* mice [124], thus contrasting with the genotype/phenotype correlation derived from DMD children [109, 110]. Although these differences between the two mutants have not yet been clarified, it is suggested that compensatory mechanisms such as the absence of the downregulation of β-dystroglycan normally observed in DMD patients, or an upregulation of certain utrophin homologues may occur [123, 126, 127]. These compensatory mechanisms may be more efficient in *mdx*^{3Cv} mice because the lack of all protein products of the gene may facilitate the access of structural homologues to specific binding sites in the inner membrane.

Given the potential role of cytoskeletal proteins in neural plasticity, the question then arose as to whether the behavioural deficits observed in *mdx* mice may be due to specific alterations in synaptic plasticity. The early finding that CA1 hippocampal neurons in *mdx* mice are more susceptible to hypoxia-induced reduction in synaptic transmission [104] suggested a critical role for dystrophin in synaptic function. Two different studies, however, showed no major deficits in LTP in CA1 or the dentate gyrus in *mdx* mice, at least one hour after induction [122, 123], a result which parallels the unimpaired performance of *mdx* mice in spatial learning. However, Vaillend and colleagues [123] found that the level of potentiation in the CA1 region of the hippocampus is transiently enhanced in *mdx* mice during the first minutes after LTP induction, despite the lack of effect on LTP maintenance. This abnormal change was not observed in *mdx*^{3Cv} mice, suggesting again the existence of specific compensatory mechanisms in these mice. Further studies confirmed that NMDA receptor-mediated short-term potentiation of excitatory neurotransmission in *mdx* mice is consistently enhanced in response to various stimulation paradigms, and showed this to be due to a reduction of the voltage-dependent block of this receptor by Mg^{2+} ions [128]. The molecular mechanisms underlying this alteration in NMDA receptor properties are unknown. They may be caused by altered functional interactions between dystrophin/DAG complexes and actin-binding proteins associated with the NMDA receptor (e.g., [129]), or by the observed deficiency in the water transporter aquaporin-4 [130] which may modify the cell response to osmotic stress and indirectly alter the cytoskeleton-dependent mechano-sensitive properties of NMDA receptor channels ([131]; but see [132]). A more likely hypothesis, however, derives from the recent finding that the clustering of $GABA_A$ receptors ($GABA_A$-R) is reduced in *mdx* mice [116], suggesting that dystrophin is required for the formation of clusters of a sub-population of $GABA_A$-R at inhibitory synapses. If this is the case in the hippocampus of *mdx* mice, then a decrease in inhibitory input from a subset of abnormally clustered $GABA_A$-R could lead to partial disinhibition of glutamatergic neurons, resulting in an enhanced NMDA receptor activation. In support of this hypothesis, Vaillend and Billard [133] showed that the $GABA_A$-R antagonist, bicuculline, increases basal neurotransmission in control, but not in *mdx* mice, suggesting a reduced sensitivity of dystrophin-deficient neurons to the antagonist. Further, they showed that both short-term potentiation (STP) and depression (STD) at glutamatergic synapses are enhanced in *mdx* mice in a bicuculline-sensitive manner. These results suggest that a decrease in inhibitory input, perhaps due to impaired $GABA_A$-R clustering, may lead to partial disinhibition of neuronal cells, thereby facilitating NMDA receptor activation and altering synaptic function in dystrophin-deficient neurons, which opens new directions to a better understanding of the neural basis of the cognitive deficits associated with DMD.

Thus, the dystrophin-deficient *mdx* mouse appears to be a rare model of a human neuropathology associated with selective alterations of inhibitory neurotransmission, abnormal short-term synaptic plasticity and impairments in certain forms of learning. Systematic investigations of the functional role of dystrophin-gene products, dystrophin homologues and DAG complexes are yet to be carried out however, and would certainly benefit from the development of new genetic models with specific and/or conditional mutations in the dystrophin gene.

Alzheimer's Disease

Alzheimer's disease (AD) is an age-related and irreversible disorder, characterised by memory loss and confusion at the clinical level. The onset of the clinical syndrome is insidious, starting with very mild, almost unnoticeable short-term memory problems and forgetting. In the most advanced stage there is loss of all stored memories (see [134] for a description of the seven stages of the clinical syndrome). The disease is believed to be due to the breakdown of neuronal connections, neuronal loss,

brain atrophying, increases in inflammation and oxidative stress and general malfunctioning of many proteins and genes involved in normal brain homeostasis and function. There is growing evidence to suggest that the pathology starts manifesting itself in the hippocampus and with the passage of time the pathology spreads to all regions in the cortical mantle [135]. Despite the massive breakdown in brain function, the only two definitive neuropathological markers of AD are the senile plaques and the neurofibrillary tangles. The senile plaque is a dense core of proteinaceous material that is generated by the β-amyloid (Aβ) peptide; when the precursor protein APP is cleaved by β and γ-secretases, it releases the entire Aβ peptide alone into the extracellular space (see review by [136]). It is now known that the N-terminal part of the Aβ peptide is cleaved first by the β-secretase, known as BACE and is then subsequently cleaved in the membrane by the γ-secretase. The presenilins, polytopic transmembranal proteins have been identified as forming part of the γ-secretase complex along with Nicastrin, which modulates γ-secretase activity. Once the peptide has been released into the extracellular space, it forms β-pleated sheets, starts to aggregate into proteinaceous material surrounded by microglia, forms a dense core and eventually burns itself out.

Less is known about the formation of neurofibrillary tangles, but this develops primarily by the abnormal hyperphosphorylation of the protein tau expressed in the axons, that aggregates into abnormal filaments, known as paired helical filaments (PHF) in the cell body [137]. Up until more recently, there was no evidence to suggest there was any connection between the formation of the senile plaque and the neurofibrillary tangle, and as there seemed to be a better correlation with the presence of the neurofibrillary tangle and the clinical syndrome, it was thought that the senile plaque played a less pertinent role in the development of the cognitive decline. A growing body of evidence, however, is now suggesting that the senile plaque may give rise to the development of the neurofibrillary tangles [138-140].

Despite having a similar clinical and neuropathological profile, AD patients have been classified as either having an autosomal dominant familial form of the disease (FAD) or a sporadic form of the disease (SAD). FAD seems generally to have an early onset, which can start in the 4th decade of life, whereas the sporadic form tends to have a later onset, often after the age of 65. FAD has been shown to develop largely from mutations in the genes encoding APP and the presenilins 1 and 2 (PS1, PS2). Much of this evidence has arisen out of sequencing the genes in families that have shown a hereditary form of the disease, however only one of the six mutations in APP has been linked to more than one of the families with AD, of European and Japanese origin. More recently, mutations in the presenilin genes have been observed in over 50 families of different ethnic origins (see [141]). Mutations in all three genes give rise to an increase in the levels of Aβ42/43. However, the familial form of the disease represents only a small proportion of the AD, with the majority of the cases being described as a non-genetic, sporadic form of the disease.

SAD occurs with no obvious mendelian-inherited abnormalities, and yet patients with this form of the disease display essentially the same clinical and neuropathological profile. Certain biological and environmental risk factors have been identified that may contribute to the development of this form of the disease. One of the most important genetic risk factors is apolipoprotein ε4 (Apoε4), a lipoprotein that is synthesised in the brain by astrocytes and is thought to be involved in the mobilisation and redistribution of cholesterol and phospholipids during membrane remodelling associated with synaptic plasticity. The Apoε4 allele shows a dose-dependent increase in the risk for AD, and has been estimated as much as a 50% risk for AD. Environmental risk factors include brain damage, stroke and more recently it has been shown that increased blood cholesterol levels may constitute a risk factor. Other environmental factors may include low education, exposure to toxic substances, including alcohol [142, 143].

The recent development of transgenic mice overexpressing mutated forms of the four major genetic risk factors of AD, APP, presenilin, tau and Apoε4 and the use of synthetic amyloid peptides have provided valuable evidence necessary for understanding the particular role of each of these genes and proteins in the development of the pathology. That which has been gleaned to date has been that mutated APP induces an age-dependent increase in deposits of amyloid (see [144, 145] for example reviews). Mutated PS1 also induces amyloid deposits, but this is not age-dependent [146-148], however when crossed with APP transgenic mice there is an acceleration of the formation of amyloid plaques [149]. In contrast, crossing APP transgenic mice with conditional null mutant PS1 mice results in an attenuation of the formation of amyloid plaques [150]. Single mutated tau transgenic mice show abnormal phosphorylation of tau and axonal abnormalities, but not the presence of neurofibrillary tangles [151] and Apoε4 transgenic mice show impairment in axonal transport and gliosis in the brain [152]. Although Apoε4 is not linked directly to FAD, mutations of the gene constitute a considerable risk factor that increases the potential for developing late onset AD [153, 154]. When crossed with certain APP mutant mice, the mutation enhances the formation of mature plaques [155] and Apoε4 null mutants reduces amyloid deposits in APP transgenic mice [156].

None of the transgenic mice to date, either as single or double transgenics, have shown the development of the full-blown neuropathology of AD,

in particular lacking the presence of the neurofibrillary tangle and the loss of cells. The assessment of potential deficits in learning and synaptic plasticity is still very much in its infancy and is not in the least consistent. In general, deficits have been observed in APP transgenics and APP-PS1 double transgenics, and these are mainly of the type that is dependent on hippocampal function such as spatial learning [157-159] and short-term or working spatial memory [158, 160]. Hsaio and colleagues [161] have shown subsequently that the deficits occur before the formation of amyloid plaques. However, the same memory deficits in the same transgenic mice have not been reported by others [162, 163]. In addition, certain sensorimotor abnormalities have been reported. Alone, PS1 transgenic mice show no impairment in spatial learning [164], but when crossed with APP transgenics, the mice display impairment in spatial learning and the impairment has been shown to correlate with age and deposition of amyloid [165-167]. There are much fewer studies of synaptic plasticity in these mutant mice and the data are contradictory as to whether there is a deficit in basal synaptic transmission [168, 169] or whether synaptic plasticity is impaired independently of normal synaptic transmission [160, 170]. These discrepancies are suggested as being due to variables such as the type of mutation and the level and location of APP expression [161].

Another approach that has been used to gain insights into the role of the senile plaque in the memory deficits associated with AD has been to inject synthetic Aβ peptides into the brain. Although many studies on the effect of the peptides on learning have been reported, the results have been somewhat confounding due to many variables in terms of the length of the peptide used, the time allowed to elapse between injecting the peptides and behavioural testing, whether soluble or aggregated peptides were injected into the brain, and perhaps more importantly whether there is in fact a presence of aggregated β-amyloid material that is induced in the brain ([171], for a review). As with the studies in transgenic mice, there have been no systematic and clear analyses of the types of memory deficits observed with injections of Aβ peptides.

In our own research we injected a combination of the Aβ40 and the Aβ43 length peptides in rats in an attempt to induce localised β-amyloid pathology in the dentate gyrus of the hippocampus [172]. This was based on an hypothesis by Jarrett and Landsbury [173] who postulated that small quantities of the longer Aβ43 peptide could act to nucleate the formation of aggregated amyloid if in the presence of metastable levels of the more soluble peptide Aβ40. We found that the combination of peptides did in fact induce aggregated amyloid material near the injection sites distributed along the dentate gyrus, together with a widespread inflammatory reaction. Using a battery of learning tasks, we found that the behavioural deficits that were induced were modest but extremely reproducible and restricted to a working memory type deficit, which is in keeping with the early phases of the clinical syndrome of AD. Neuronal transmission and plasticity was then examined to characterise the physiological impact of the generation of aggregated β–amyloid deposits. The findings showed that the initial induction of LTP in the dentate gyrus was not affected, but its maintenance was, as it declined back to basal levels within three hours in much the same way as it declines in aged rats. These results suggest that the formation of aggregated amyloid plaques and inflammation in the dentate gyrus lead to cognitive deficits similar to those observed in the early stages of AD, via malfunctioning in the capacity for long-lasting neural plasticity. In a subsequent study, Walsh et al [174] have shown a similar time course in the decay rate of LTP in CA1, produced by intracerebroventricular infusion human Aβ oligomers that are known to induce neurotoxicity without the formation of mature plaques. Thus, the two approaches, the transgenic mice and injecting amyloid peptides, act in complement with each other, the former bringing important information relating to the aetiology of the disease and the later bringing important information as to understanding how, at least the amyloid peptide may contribute to the memory deficits. Although behavioural, electrophysiological and molecular biological studies are still very much in their infancy, these two animal models provide invaluable tools for understanding the molecular and cellular basis of the memory decline in AD.

POTENTIAL STRATEGIES FOR AMELIORATING COGNITIVE DECLINE IN AGEING AND PATHOLOGICAL DISEASES

Clearly one of the most pressing issue with learning and memory dysfunction associated with age or diseases is how can we prevent or slow down these deficits. The search for potential rescue strategies, however, is still at a very early stage. Far too many questions remain about the biological role of specific genes and proteins, about the relationship between defined molecular mechanisms and their physiological role in neural network functions, and about the relationship between these mechanisms and cognitive functions. Although still a distant goal, new knowledge about some of the key mechanisms underlying learning and memory may be of inestimable value in enabling the development of novel therapeutic or rescue strategies. Here we describe a few recent attempts at exploring the potential for compensating the memory deficits observed in ageing and in animal models of DMD and Alzheimer's disease.

In Alzheimer's disease, two novel approaches have been recently developed in an attempt to

reduce the development of the senile plaques in AD and ameliorate cognitive deficits; inoculation with β-amyloid to prevent the development of, or eliminate existing senile plaques in the brain, and chronic treatment with non-steroidian anti-inflammatory drugs to reduce the level of inflammation associated with pathological signs of AD. Inoculation of human Aβ42 in APP transgenic mice has resulted in the prevention of the formation of amyloid plaques if injected early enough, and has stemmed the further development of plaques when already present in older mice [175]. In addition, behavioural studies have also shown an amelioration of the memory deficits normally observed in APP transgenic mice [176, 177]. It was believed that the inoculation of β-amyloid activated the autoimmune system to attack amyloid plaques and lead to testing the compound in clinical trials. Trials have been currently suspended, however, due to the adverse development of inflammation in some of the patients. It has been suggested that the autoimmune system may also target APP, the amyloid precursor protein, which is found in many normal healthy cells including neurons and may have important function for cell-to-cell communication [178].

The other approach for stemming the development of AD pathology and cognitive deficits has been the chronic use of non-steroidian anti-inflammatory drugs (NSAIDs). One of the major neuropathological markers of AD is the extensive inflammation in the brain. During the evolution of the senile plaque, reactive microglia and astrocytes typically surround it and each are capable of triggering multiple independent pro-inflammatory signalling cascades. Epidemiological studies have shown that there is as much as a 50% reduction in the risk of AD associated with the chronic consumption of NSAIDs [179-181]. In transgenic mice, it has been shown that ibuprofen, the most commonly used NSAID, and the Indian spice curcurim, can reduce the size and number of amyloid plaques and reduce the levels of activated inflammation [182, 183]. In our own studies where we have induced aggregated amyloid deposits in the hippocampus with a combination of the Aβ40 and Aβ42 peptides, we have found that chronic treatment with the NSAID indomethacin rescues the deficits in hippocampal synaptic plasticity and, concomitantly, the learning deficits [184]. Although the efficacy of NSAID treatment has been questioned in the human studies, our understanding of the role of inflammation in the cognitive decline in AD in rodent studies may prompt the development of more efficient anti-inflammatory treatment for humans.

In DMD, despite the encouraging progress made in the search for treatments to reduce muscular degeneration, different therapeutic approaches including pharmacological treatments, cell transplantation and efficient regulated gene transfer have met with little success and no definitive treatment has yet been discovered [185-187]. Advances in dystrophin gene therapy faces important obstacles and most success has been achieved with truncated dystrophin minigenes, with the hope of converting a DMD phenotype into that of the milder BMD. Although ambulation would be retained for a longer period with this approach, it remains unsatisfactory and may not provide a solution for the cognitive impairment. Alternative approaches that have been explored, including the possible upregulation of genes such as utrophin, have also met with limited success [188]. Although gene delivery to the brain may find applications in some neurodegenerative disorders [189], it is far too early to consider this approach in DMD. Nevertheless, neurons express a large array of short products homologous to dystrophin and utrophin, in contrast to skeletal muscles cells in which only the full-length products of the genes are present. Some of these dystrophin structural homologues appear to be regulated in mutant mice lacking dystrophin gene products [127]. Investigating the complex functional interplay of these proteins in normal brains and their modulation in mouse models of DMD is therefore of potential importance both for the understanding of the molecular genetics of the cognitive deficits and for the discovery of candidate compensatory mechanisms. Among the collection of data accumulated from studies in DMD mouse models, the characterisation of electrophysiological abnormalities such as the altered GABA function suspected in the brains of *mdx* mice, may also be most relevant to the clinical condition because it may provide a scent towards key targets for pharmacological approaches.

Another conceptually different, yet genuinely attractive approach that has recently been given much attention is an environmentally based rescue strategy. This is based on a behavioural model, the enriched environment paradigm, initiated by Hebb's pioneer observation that rats which he had brought home for some time and later returned to the laboratory showed better problem-solving ability than rats that had remained in the laboratory. In this model, adult animals are allowed to explore a large open-field containing a variety of toys, exercise wheels, small houses or tunnels each day for a limited period, thus facing a complex range of sensory, in particular visual and spatial, motor and social stimuli. It has been known for decades that experience in an enriched environment consistently improves both learning and brain plasticity in the adult (reviewed in [190, 191]). In rodents, experience in enriched environments improves performance in various learning tasks with a spatial demand [192-196]. More recently, Rampon and colleagues [197] reported that enriched experience also enhances memory performance in adult mice tested in several different non-spatial memory tasks, suggesting a broad effect on different categories of memory. At the cellular level, several studies have concomitantly shown that experience in an enriched environment results in various neurochemical and anatomical

changes in the rat brain as well as in many other species including birds, ground squirrels, cats or monkeys (reviewed in [198]). Among these are gross anatomical changes such as thicker hippocampus and cerebral cortex and larger neuronal soma and nuclei [199-201]. Certain neural mechanisms have been identified as being targeted by behavioural enrichment which include an increase in acetylcholinesterase activity [202], in the complexity of dendritic arbours and synaptic density [203, 204], and prevention of synaptic loss [205]. Changes have been observed in neurons of the cortex [206-208], hippocampus [197, 209], striatum [210] and cerebellum [211]. Another, intriguing consequence of behavioural enrichment is in the production of new cells in the adult brain. Although initial studies in the cortex revealed only increased gliogenesis after enrichment [212], mainly attributable to oligodendrocytes [213], more recent investigations have shown that enriched experience increases the number of new neurons in the dentate gyrus of the hippocampus [195, 196]. This effect on adult neurogenesis is presumably due to an enhanced survival of newly generated cells rather than to a higher proliferation rate [195] and is accompanied by reduced apoptosis [214], suggesting an activity-dependent protective effect on neuronal survival. These studies thus suggest that behavioural experience in an enriched environment increases the complexity and possibly computational properties of neuronal networks, thereby enhancing information processing and memory formation. At the physiological level, enrichment has been shown to modify synaptic transmission in the hippocampus [215, 216] and to result in an increased capacity for LTP [217]. Although no direct link has yet been provided, the reported increase in the expression of genes encoding the growth factors, GDNF [214], NGF [218, 219] and BDNF [214, 220], or of the LTP-related immediate early genes *zif268* and *Arg3.1* [221, 222], suggest that the behavioural enrichment paradigm may lead to a common thread towards a more general compensatory strategy for rescuing at least in part the cognitive deficits caused by different types of diseases known to be associated with an altered LTP. Moreover, a more extended search for enrichment-induced gene transcription in the cortex using DNA microarrays has recently revealed changes in the expression of a variety of genes, many of which can be linked to neuronal structure, synaptic signalling and plasticity [223].

Research over the past years has firmly established that behavioural enrichment can rescue the cognitive deficits associated with a variety of pathologies or brain damage. For example, learning and memory deficits induced by hippocampal [224-226], cortical [224, 227, 228] or fimbria-fornix [229] lesions are alleviated by pre- or post-lesion environmental enrichment. Enrichment also protects against seizures and excitotoxic injuries [214] and reduces the behavioural deficits that follow perinatal asphyxia in rats [230]. A beneficial effect of behavioural enrichment has also been shown in mouse strain of the 129/Svj background that are typically classified as poor learners, and the amelioration of learning is associated with increased neurogenesis [231]. To assess the potential of behavioural enrichment in the rescue of memory deficits resulting from dysfunctional LTP in the hippocampus, the effects of enrichment was examined in conditional-knockout mice in which the R1 subunit of the NMDA receptor was selectively deleted in area CA1 of the hippocampus. These mice lack LTP in area CA1 and have severe deficits in several memory tasks [37]. We found that after two months of daily training in an enriched environment, the learning deficits of the knockout mice tested in three different memory tasks were either largely or completely rescued [197]. Furthermore, behavioural recovery was associated with a higher synaptic density in the hippocampal CA1 area of these mice after enrichment.

Can behavioural enrichment or manipulation ameliorate the memory deficits in ageing, Alzheimer's disease or DMD ? In DMD, potential therapeutic strategies liable to improve the quality of life of DMD children and their relatives include parental guidance, speech therapy, psychotherapy and neuro-rehabilitation. As pointed out by Hinton and colleagues [96], some of the mild deficits common across DMD patients, in particular those affecting working memory, may be partly compensated by learning strategies relying on rote memory and non-verbal methods. This approach, however, may not apply to the most severely affected individuals, or in the case of certain specific mutation patterns. Mouse models of DMD may prove useful to evaluate the relevance of behavioural strategies to compensate for the learning deficits. For example, *mdx* mice display weaker deficits in bar-pressing learning when they are submitted to a behavioural test battery before acquisition of the task [106], as compared to naïve *mdx* mice [124]. This suggests that the magnitude of the learning deficits depends on the animal's own experience and may be reduced by environmental experience. Furthermore, *mdx* mice have severe memory deficits in tasks that require only a few trials [105] whereas they are not impaired in tasks requiring extended training, such as with spatial learning [122, 123]. This suggests that overtraining may be beneficial to learning in *mdx* mice. The potential impact of environmental enrichment and overtraining, however, needs to be experimentally verified, and would be best illustrated if compared among different mouse strains showing selective deficits associated with disrupted expression of distinct dystrophin gene products.

As ageing is the most important risk factor in AD, understanding what potential environmental influences may be associated with age-related memory deficits becomes important for both pathological and non-pathological ageing. In normal or non-pathological ageing, no single factor can

account for the deficits and both the biological alterations and the memory deficits tend to vary from one individual to another. Although many factors influence our well being during the course of life, two major factors, environmental enrichment and dietary restriction have been shown to have a beneficial impact in ageing. Studies in which a dietary restriction has been placed on mice or rats have shown that a 30% restriction results in an extension of life span by 30-40%, a greater resistance to kainic acid-induced hippocampal damage, and preservation of memory [81, 232]. In addition, dietary restrict imposed on APP transgenic mice at an early age appears to result in a reduction of Aβ deposits in the brain [81]. It has been suggested that dietary restriction produces a mild stress response which results in the activation of several genes that repress oxyradical production and stabilise calcium homeostasis [81]. In fact both environmental enrichment and dietary restriction share some of the same mechanisms of protection against neuronal degeneration both in non-pathological ageing and in reducing the risk of developing AD. There also is a wealth of studies which have shown that aged rats spending time in an enriched environment show better learning and memory capacities than aged cohorts that have not [233, 234]. For example, both the spatial [235] and non-spatial [236] memory deficits observed in old rats are significantly reduced after experience in an enriched environment. The effect of enrichment appears to be durable as exposure to an enriched environment early in life leads to a reduction in later age-related memory deficits. The underlying mechanisms, however, are not known. Recent studies showed that enriched rearing conditions reduces ageing-induced gliosis in the hippocampus [236] and can restore the age-related decrease in synaptophysin content in synapses, suggesting compensation of some of the altered synaptic plasticity mechanisms [237]. Neurogenesis may also be a contributing factor, for neurogenesis in the dentate gyrus of the hippocampus continues in senescent mice and can be stimulated by living in an enriched environment [231].

The available evidence thus suggest that extended training, certain environmental conditions and in particular environmental enrichment, can override some genetic constraints, and lead to enhance functional and structural brain plasticity, resulting in an improvement in memory performance. Corroborative evidence from epidemiological studies in humans has shown an inverse relationship between the level of education and the potential risk of AD [238, 239] or of Parkinson-related dementia [240], as does lower caloric intake in AD [241] and Parkinson's disease [242]. Clearly, the observation that environmental enrichment has beneficial effects on learning and memory in normal or aged animals or after brain damage or injury, suggest some resilience to neurodegenerative diseases. In a study in mice carrying the Huntington's disease transgene, it was shown that enrichment delays the onset of behavioural deficits [243]. Similar approaches, however, remain to be carried out in other animal models of human diseases in order to explore their behavioural impact and the underlying cellular and molecular mechanisms.

The past decade has seen significant advances in our understanding of some of the key cellular and molecular mechanisms of brain plasticity and memory formation and has provided substantial evidence connecting biochemical and molecular mechanisms of plasticity to the laying down of memories. Recent research in animal models has then provided promising inroads into testing potential therapeutic strategies, whether based on environmental manipulation or on more molecular-oriented and disease-specific strategy. We feel that although an ambitious and distant goal, combining these in a multidisciplinary approach based on molecular, system and cognitive neuroscience may be of inestimable value in enabling the development of novel therapeutic strategies.

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