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Neural plasticity: changes with age

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Summary. Changes in the number, type and function of nervous system connections, in the morphology and function of glia and in neuron-glia interactions, are at the basis of vertebrate adjustment to changing environmental and physiological conditions. Collected under ''neural plasticity'', these age-dependent changes underlie adaptations apparently as different as the physiological response to dehydration or learning, and its electrophysiological and morphological correlates.

Keywords: Learning, LTP, LTD, synapse renewal, axon sprouting, hebbosome, dendritic spines.

Abbreviations

CNTF ciliary neurotrophic activity, *EC* enthorrinal cortex, *ECL* enthorrinal cortex lesion, *LTD* long term depression, *LTP* long term potentiation, *NPF* neurite promoting factor, *NTF* neurotrophic factor, *PNPF* poly-ornithine-bindable neurite promoting factor.

Introduction

The term *plasticity* was introduced in 1890 by William James to describe the susceptibility of modification of human behaviour. It was also used by Marinesco (1907) and Minea (1909) in their work on transplantation of sensory ganglia, to describe the changes in morphology undergone by the transplanted neurons. Cajal was aware of their work, and believed that the behavioral modifiability reported by James must have an anatomical basis, as reported by Marinesco and Minea (Ramón y Cajal, 1914). However, after Cajal's death researchers adopted a rigid view of the adult central nervous system (CNS), assuming that once development had finished, CNS anatomy was unchangeable, except for degenerative processes. Against this general view, Liu and Chambers showed in 1958 that axonal sprouting occurred in adult CNS and

overwhelming evidence has accumulated in the last three decades confirming their finding. The nervous system maintains throughout life the capacity of functional and anatomical modification. The neuronal networks that make up the nervous system of mammals remain plastic, modifiable, during their whole lifetime and plasticity is one of their main adaptations. *Neural plasticity* must be understood as a tissue property that belongs to neuron-glia ensembles. Its existence is no longer questioned and its cellular and molecular bases are the object of intensive research. The stimuli that induce neural plasticity are all kinds of experiences, environmental pressures, physiological modifications, or lesions. We propose that the cellular and molecular processes that govern neural plasticity are the same, regardless of the precise activity involved. We present in this Chapter a general view of plasticity, its origin, function, mechanisms, changes with age and possible clinical manipulation. If neural plasticity mechanisms in the CNS apply generally, regardless of the precise activity involved, then we may use the information on the physiological principles that apply to learning, an activity mammals are quite good at, to enhance the limited mammalian CNS repair capabilities.

Neurons and glia: a unit of function

The main cell types in nervous tissue are neurons and glial cells. Neurons are cells highly specialized to rapidly receive and transmit messages. They have a relatively small body and multiple ramifications that cover an extensive surface, allowing them to maximize inter-communication. The human brain contains more than ten thousand million neurons; the cerebellum, between ten and one hundred thousand million. The *synapses* or 'synaptic contacts', are the sites where a neuron transmits its message to another neuron. A typical CNS neuron frequently receives tens of thousands of synaptic contacts, although cerebellar Purkinje cells may receive up to 200.000. Connections between neurons give rise to neuronal circuits and neural plasticity is, to a large extent, synaptic plasticity, that is, the susceptibility of modification of the type, form, number and function of the synapses, hence, of the neuronal circuits. Processes as diverse as learning and memory, the response to physiological situations such as pregnancy or thirst, and the response to lesions, have as a common basis synaptic plasticity and neural plasticity.

Today's consensus is that nervous tissue function can be understood only taking into account the other cells characteristic of this tissue, the glial cells. Their number exceeds that of neurons about 10-fold and constitute about half the nervous tissue mass (Pope, 1978). The original description of glia by Virchow in 1859 as nervous glue, conferred glia a static image, maintained mainly by neuroanatomists and neuropatathologists the following 100 years. This view has changed noticeably during the last 25 years and nervous function, dominated by the neuronal point of view, has widened to another where neural development, nervous activity, its maintenance and pathology, are examined from the perspective of a unit of function neuron-glia (Fig. 1A). The idea of a dynamic unit of function neuron-glia has been proposed independently by various researchers in the last 20 years, but has been formulated explicitly in detail by Arenander and de Vellis (1983) and, later by Nieto-Sampedro (1988a).

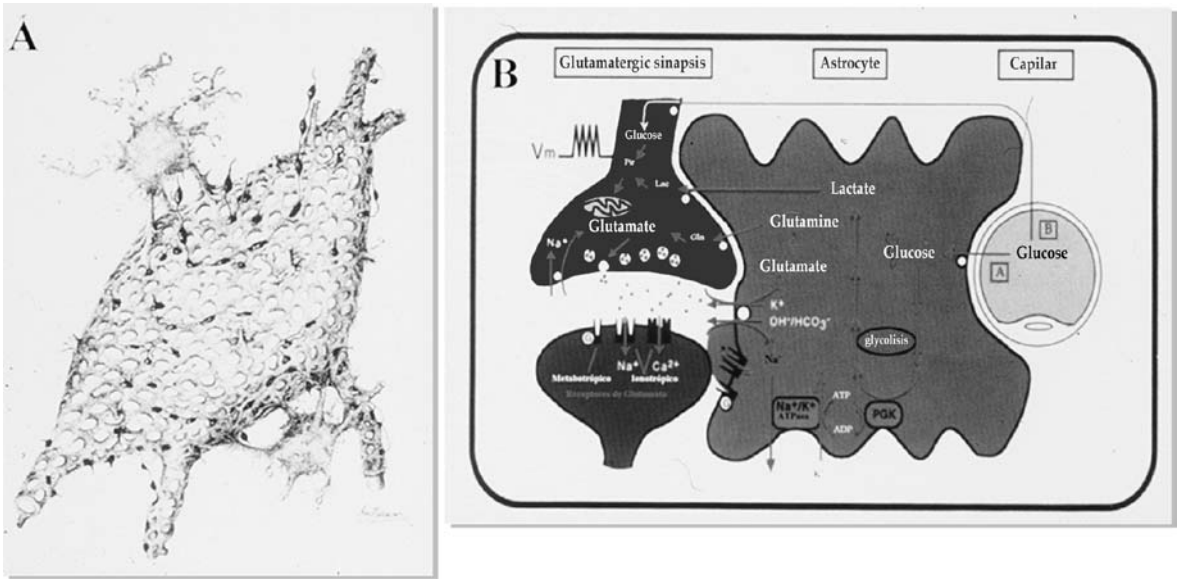

Fig. 1. Morphological and functional images of the neuron-glia unit of function. **A** The image obtained by Lafarga et al. (1984) after three-dimensional reconstruction of thin serial sections of the fastigial nucleus of the cerebellum, stained specifically for glia, was that of a neuron enveloped in a net of astrocytic processes (blue). The holes in the net are synaptic sites. **B** The complementary functions of the main cellular components of the tissue, neurons, glial cells and blood capillaries, account for nervous system plasticity

The glial types in the CNS are astroglia, oligodendroglia and microglia of which those more directly related to neural plasticity are probably astroglia and microglia.

Astrocytes are intimately associated to both neurons and to the whole organism. They envelope central synapses and form the *glia limitans*, boundary between the CNS and the other tissues, particularly blood vessels, in intimate contact with which are placed their end feet high conductance regions (Newman, 1986). Thus, astrocytes monitor the blood content of nutrients, oxygen, vitamins and hormones. They are sensitive to ions, specially potassium and can bind, transport and metabolize neurotransmitters. Astrocytes respond to excitatory neurotransmitters by despolarizing and some may conduct action potentials (refs. in Arenander and de Vellis, 1983; Nieto-Sampedro, 1988a; Fig. 1B). In addition, they all are intercommunicated directly by ''gap-junctions'' and similar mixed junctions probably relate them to neurons (Sontheimer, 1995). As found by Smith's team (Cornell-Bell et al., 1990), astrocytes intercommunicate also by means of Ca^{2+} 'waves', which affect intracellular Ca^{2+} concentration in the neurons in contact with them (Nedergaard, 1994). Besides, astrocytes synthesize the most abundant CNS excitatory neurotrasmitter, glutamate, store it and liberate it in a non-vesicular manner (Parpura et al., 1994). They also synthesize NO, a highly diffusible neuromodulator (Garthwaite, 1991; Murphy et al., 1993) that strongly affects both neuron and astrocyte physiology. All these properties make astrocytes capable of continuously monitoring (detecting, receiving and interpreting) the activity of neurons and

modifying it as necessary. Astrocytes function as feedback controllers of the neural environment, with set point to the normal neuronal activity. Any modification of the normal tissue composition triggers compensatory glial responses, for example, by eliminating excess neuroexcitatory molecules before they reach excitotoxic levels, or by producing neurotrophic factors that allow effective buffering of intracellular Ca^{2+}, avoiding neuronal apoptosis.

There is less information on the cell biology of microglia, although great progress has been made in the last decade and it certainly plays an essential role in communicating nervous and immune systems (see Microglia, 1993).

To summarize, nervous tissue is made up of functional units consisting of societies of groups of neurons and glial cells. Glial cells are the controllers of the environment of these dynamic ensembles as regards ionic composition, neurotransmitter levels and growth factor supply. The response of nervous system to perturbations can be correctly understood only as the coordinated reaction of these cellular ensembles. We will review what we think key points in neural plasticity, pointing at those known or suspected to be particularly affected by age.

Neural plasticity and synapse renewal: changes with age

The functional and anatomical modifiability of the nervous system is to a large extent the plasticity of the networks that make it up, which remain modifiable during the whole lifetime of the organism in response to all kinds of experiences. The experiences may be environmental pressures, lesions or physiological changes, associated for example to aging. The essential elements of neural networks are the connections between their neuronal elements, the synapses and much neural plasticity is synaptic plasticity. The maximal expression of synaptic plasticity is observed during developmental synaptogenesis, when synapses go through cycles of formation and regression. One of the most elegant examples of synaptic plasticity was observed by Clark C. Speidel, in the sensory endings of the living tadpole (Speidel, 1941). Speidel observed in the same sensory arborization, resting terminals, growing terminals and nerve endings in frank regression. Depending on time and environmental conditions, some resting terminals became growth cones and some growth cones became stable or degenerating terminals. In summary, what Speidel observed was that, in the developing nervous system, synapses were dynamic structures.

The renewal or turnover of synapses is maintained in adult mammals in a more limited manner, yet still sufficient for changes in type, form and/or number to mediate physiological and behavioural adaptations. Renewal of a synapse population implies breaking a set of synaptic contacts and substituting them by new ones. These are population changes and, individual synapses may disappear without being substituted, or a new synapse may form where there was none before. However, in general, the renewal process includes four stages: 1) disconnection of synapses; 2) initiation and growth of new axons; 3) formation of new synaptic contacts y 4) maturation of the new synapses, i.e., appearance of synaptic vesicles and pre- and post-synaptic densities. In every of these steps glia may or must intervene actively and this is one of the sources of age dependence.

The presynaptic terminals that take part in synapse turnover arise from pre-existing axons, in a process called axon *sprouting*. Axon sprouts are named depending on their point of origin in the axon: sprouts called *terminal or ultra-terminal*, are extensions of the presynaptic terminal. The sprouts called *collateral* arise as a new axonal branch and are named *nodal* if they originate from the node of Ranvier of a myelinated axon. A sprout that is the renewed continuation of an axon stump is denominated a *regenerative* sprout. Axonal sprouting is independent of subsequent synapse formation. In fact, in the CNS sprouts frequently degenerate and never form synapses. The term axon sprout simply designates a type of growth response. It may or may not be the first step in the formation of a new synapse.

Synapse renewal is an important aspect of neural plasticity with possible evolutionary implications. Greater capacity for synapse renewal means greater nervous circuit plasticity, an advantageous adaptation of a nervous system that may facilitate its selection. A clear example of both, function of neuron-glia ensembles and the adaptive advantages that efficient synapse renewal gives mammals relative to other vertebrate classes, is the pituitary regulation of the state of hydration, parturition or lactancy. The secretory axons of the neurohypophysis originate in the magnocellular neurons of the supraoptic nucleus of the hypothalamus and terminate in the spaces surrounding fenestrated capillaries, where they discharge their secretion products, hormonal peptides. The actions of two of these peptides, oxytocin and vasopressin, are well characterized, controlling water retention and smooth muscle contraction. The neurons of the supraoptic nucleus of well hydrated female rats that are neither pregnant nor lactating, are separated from one another by astrocytes. Similarly their axonal endings are isolated from capillaries by pituicytes, a glial type surrounding these terminals. Water deprivation for four or more hours, lactancy or advanced pregnancy stages or parturition, initiate the following cascade of events: (i) withdrawal of glial processes and, consequently, appearance of contacts among cell bodies and dendrites of neighbouring neurons, leading to electrotonic coupling; (ii) the appearance of synaptic contacts between adjacent magnocellular neurons; (iii) the retraction of pituicytes, thus allowing axon terminal access to perivascular space; (iv) the substitution of the slow, irregular electrical activity of supraoptic neurons by continuous rapid rhythmic activity, with occasional high frequency discharges; (v) the synthesis of proteins, particularly the hormones previously mentioned and their precursors. All these changes occur concomitantly with the appropriate physiological response (i.e., water retention in the kidneys or mammary pressure increase), are completely reversible and allow the organism exhibiting them successful survival and reproduction in environments of variable humidity (Hatton, 1985).

Synapse renewal and LTP

The natural stimuli for synapse renewal more frequent in mammals are those that induce learning and memory. Exposure to these stimuli may last a very short time, but perceptions made during seconds or tenths of a second may be remembered many years later. The main questions in learning and memory

studies are, on the one hand, the mechanism of its formation, that is, how a brief stimulus is translated into a long-lasting neural record and the nature of that record or 'engramma'. A widely held belief is the synaptic plasticity and memory (SPM) hypothesis (Martin et al., 2000). The SPM hypothesis proposes that repeated physiological activation of a *hebbian synapse* is translated at a later moment into a morphological change in that synapse. The same processes that increase the efficiency of the synapse, causes a morphological modification that ensures a record of long duration. This field of research is, of course, very active and open to controversy and presenting the SPM here is just a personal preference. It was proposed by Cajal, among others, at the beginning of the XX century and is widely shared nowadays (Stryker, 1995; Malenka and Nicoll, 1999; Martin et al., 2000).

LTP: brief electrical signals drive long-lasting changes

A ''hebbian synapse'' is a synapse that behaves as proposed by Donald Hebb (1949). Hebb postulated that a synapse used repeatedly is 'reinforced', i.e. made more efficient. Once the synapse is reinforced, its stimulation threshold becomes lower and the synapse can be activated by stimuli of lower intensity than originally necessary; or activated by the same stimulus, it produces a response of greater amplitude. Bliss and his team (Bliss and Lømo, 1973; Bliss and Gardner-Medwin, 1973) recorded electrophysiologically neurons from the dentate gyrus of the rabbit that was stimulated repeatedly from enthorrinal cortex afferents and found synaptic changes as postulated by Hebb. They called this process *long term potentiation* or LTP. Indirect evidence has accumulated indicating that LTP may be the storage device for some types of memory, particularly in the hippocampus (Izquierdo and Medina, 1995; Larkman and Jack, 1995; Malenka, 1995). Other synapses in other CNS locations, as well as inhibitory synapses, may be potenciated (Marty and Llano, 1995). It seems likely that LTP may be one of the first steps in synapse renewal.

LTP is conveniently induced by simultaneous activation of a synapse population at frequencies between 20 and 200 Hz. This tetanizing stimulation provides the essential requirement of Hebb: concomitant pre- y postsinaptic activities. The strong depolarization of the postsynaptic neuron occurs at a time when the synapse still retains a concentration of neurotransmitter sufficient to act on the postsynaptic receptors. Considering the hippocampus, where the synapses capable of potenciation are excitatory and glutamatergic, presynaptically liberated glutamate acts on two types of ionotropic receptors that coexist in dendritic spines: AMPA receptors (respond preferentially to the glutamate agonist DL-a-amino-3-hydroxy-5-methylisoxazole-4-propionate, abbreviated AMPA) and NMDA receptors (that respond preferentially to the glutamate agonist NMDA). During normal synaptic transmission, the arrival of an action potential to the axon terminal causes glutamate liberation, which, acting on AMPA type receptors, mediates Na^+ channel opening. AMPA-receptor gated Na^+ channels support the majority of the depolarizing postsynaptic current. NMDA-type receptors contribute very little to postsynaptic depolarization, because at the membrane resting potential NMDA-receptor associated channels

are blocked by Mg^{2+} ions. However, when a train of stimuli depolarizes the postsynaptic membrane, Mg^{2+} dissociates from the NMDA receptor that, free, is capable of allowing passage of $Ca^{2+}$and Na^{+}. Thus, NMDA-type receptors may be considered as voltage-dependent molecular coincidence detectors, that permit Ca^{2+} entry into the postsynaptic neuron when afferent activity occurs together with postsynaptic depolarization (see, for example, Silva, 2003). There is agreement in that LTP can be initiated postsynaptically. However the relative contribution and importance of pre-synaptic modifications improving afferent efficiency, possibly increasing neurotransmitter liberation probability, is still a subject of discussion (Larkman and Jack, 1995).

Depolarization and increase of intracellular postsynaptic Ca^{2+} are both required to reinforce synaptic transmission. Additionally, two further processes appear essential to ensure durability of the potentiation. One is the additional regulation of intracellular Ca^{2+} concentration, by activation of so-called ''*metabotropic receptors*'' (Bortollotto et al., 1994; Pin and Bockaert, 1995; Simpson et al., 1995). The other is the activation of regulators of DNA transcription and protein synthesis (Malenka, 1995; Schulman, 1995). The four families of transcription factors participate in signal amplification and consolidation (Hinoi et al., 2002). In the absence of these processes, the duration of the synaptic reinforcement is relatively short lived, less than 1 hour. Metabotropic receptor activation initiates various intracellular enzymic cascades, mediated by secondary messengers, including Ca^{2+}, cyclic AMP, cyclic GMP and phospholipid degradation products, such as inositol phosphates and arachidonic acid. Some of these activities are protein kinases, that catalyze transcription factor activation by phosphorylation. When LTP is allowed to proceed undisturbed, a prompt consequence of intracellular Ca^{2+} elevation is the activation de protein kinases. Pre-synaptic protein kinase C (PKC) and postsynaptic Ca^{2+} and calmodulin-dependent protein kinase II (CaMKII) are the kinases that have received more attention. The latter of them is very abundant in dendritic spines. However, cyclicAMP-dependent protein-kinase A is probably important for long-term memory consolidation. It phosphorylates CREB, a transcription factor critical for this process also phosphorylated by CaMK IV in response to growth factors. Finally, a tyrosin kinase phosphorylates NMDA-type glutamate receptors during LTP induction (Schulman, 1995).

An electrophysiological phenomenon equivalent but opposite to LTP was observed initially in cerebellum, then in hippocampus. It is called *long term depression* or LTD (Ito, 1989; Malenka, 1995; Malinow and Malenka, 2002). LTD is induced by low frequency (1 to 2 Hz) prolonged stimulation (3 to 15 minutes) of a synapse and can reverse LTP. The mode of LTD induction is remarkably similar to that of LTP, involving, as for LTP elevation of intracellular Ca^{2+} concentration. However, the concentration increase is much lower than that after a tetanizing stimulation and instead of activating kinases, LTD activates calcineurine, a synaptic phosphatase with high affinity for Ca^{2+} (Lisman, 1989). The name LTD is reserved for induction in a naive synapse. When LTD is induced on a previously potentiated synapse, the reversion of LTP is called depotentiation (Rosenzweig and Barnes, 2003). The existence in neurons of approx. 23 Mdalton multiprotein signaling complexes, or ''hebbosomes'',

specialized in decoding patterns of synaptic activity, has been proposed by Grant and O'Dell (2003). Hebbosomes would coordinate the activity of múltiple pathways downstream from receptors, translating LTP and LTD into lasting neuronal changes. Perturbation of ''hebbosome'' formation may lead to problems of memory formation.

LTP, learning and dendritic spine changes: aging deficits

Evidence for a relationship between LTP, learning and changes in dendritic spine number and morphology, has been available for many years (Rosenzweig and Bennett, 1976; Lee et al., 1981; Greenough and Chang, 1984), but the correlation has been observed recently more directly (Crair and Malenka, 1995; Kirkwood et al., 1995; Yuste and Bonhöffer, 2001, 2004; Geinisman et al., 2001; Lamprecht and LeDoux, 2004). Postsynaptic morphological changes seem a logical consequence of the postsynaptic cell protein synthesis required for LTP stabilization. However, the mechanism of communication between pre- and postsynaptic components is less obvious. Two retrograde messengers, nitric oxide and ara chidonic acid, seem capable of informing the presynaptic terminal on the state of their postsynaptic counterpart. The first is produced by a Ca^{2+} and calmodulin dependent NO synthase (Bredt and Snyder, 1992). The second, is generated by phospholipase A_2, also Ca^{2+}-dependent (Bliss et al., 1990). Both messengers seem to act by increasing neurotransmitter liberation.

From this point onward, possible mechanisms for induction of LTP-associated presynaptic morphological changes, are more speculative. Neurotrophic factor synthesis is much increased after stimuli capable of inducing LTP and this increase is maintained up to 7 days after epileptiform stimulation (Isackson, 1995). If following our hypothesis (Nieto-Sampedro et al., 1982b), we assume that postsynaptic densities grow by addition of new material and that after they reach a maximal size they undergo fragmentation, this would be equivalent to dendritic spine division (Carlin and Siekevitz, 1983) and would generate vacant PSDs. A vacant or inactive postsynaptic site is an active producer of neurotrophic factors capable of inducing sprouting (Brown and Ironton, 1977a–c; Betz et al., 1980; Wernig and Stöver, 1979; Holland and Brown, 1980; Lömo and Slater, 1978; Aguilar et al., 1973; Diamond et al., 1976; Cooper et al., 1977; Guth et al., 1980). Stimuli capable of inducing LTP, would also stimulate synapse renewal and increase the number of vacant spines. The factors liberated at these spines, alone or together with glycosaminoglycans (Ornitz et al., 1995) or adhesion proteins (Williams et al., 1994; Doherty et al., 1995), would have the neuritogenic activity required to initiate axon sprouts, destined to occupy the vacant spines. Additionally, synaptotagmine, a synaptic vesicle protein involved in neurotransmitter liberation, promotes fibroblast filopodia formation (Feany and Buckley, 1993). These actin-rich structures are typical of pre-synaptic growth cones; elevation of pre-synaptic activity produce high levels of both Ca^{2+} and synaptotagmine, that induce ultraterminal sprouting, the kind of axon sprouting more frequent in the CNS. In contrast, the levels of Ca^{2+} produced in response to stimulation at the frequencies that induce LTD are lower, yet capable of activating calcineurin which, in turn, causes axonal growth cone

filopodia retraction (Chang et al., 1995). The tyrosin kinase PYK 2 (Lev et al., 1995) may be a key convergence point of Ca^{2+} levels regulated by electrical activity which, in turn, is regulated by neurotransmitter-governed ionic channels and by metabolic or growth signals, ruled by metabotropic receptors and growth factors.

Aging has specific effects on hippocampal physiology, plasticity and network dynamics and, consequently, on learning and memory (Barnes, 2003; Rosenszweig and Barnes, 2003). Aged rats appear to have intact hippocampal LTP induction when robust, high intensity stimulation protocols are used, but show defective induction when lower-intensity stimulation is applied. Most early experiments used long, high-frequency, high current-amplitude stimulus protocols (e.g. 50 μA at 100 Hz, for 1 sec) and showed no age-related deficits in LTP induction (Landfield and Lynch, 1977; Landfield et al., 1978). However, when fewer stimuli and/or lower amplitude currents were used to induce LTP, aged rats consistently showed LTP induction deficits (Deupree et al., 1993; Moore et al., 1993). The LTP deficits observed may arise both, from the higher intensity of the stimulus required for LTP induction in aged animals and from the faster decay of the potentiation in senescent rodents (Barnes, 1979, 2003; Barnes and McNaughton, 1980). LTP deficits correlated with aged mice poorer performance on a spatial memory task.

The memory deficits of senescent rats and mice coincided with those found in the induction and/or maintenance of NMDA-receptor dependent LTP (Rosenszweig and Barnes, 2003). However, recent work has revealed forms of LTP different from that mediated by NMDA-type receptors. By blocking NMDA receptors and applying stimuli of very high intensity in terms of frequency, duration or current amplitude, Driver and Teyler (1990) discovered NMDA-receptor-independent LTP. The potentiation observed appeared to be mediated by Ca^{2+} entry through voltage-dependent, L-type Ca^{2+} channels (VDCC), and has been called vdccLTP (Grover and Teyler, 1990). In some cases, Ca^{2+} entry through NMDA receptors is sufficient to initiate the cascade of events that lead to synaptic potentiation; in others, the combined calcium signal from NMDA receptors and VDCC participates (Grover and Teyler, 1990). Like NMDA-receptor dependent LTP (nmdaLTP), vdccLTP seems to be synapse specific, that is, only the synapses active during vdccLTP induction are potentiated. However, whereas nmdaLTP requires serine-threonine kinase activity, vdccLTP depends on tyrosine kinase (Cavus and Teyler, 1996). 'Standard' high-intensity LTP stimulation (about 100 Hz for 1 sec) would induce both, nmdaLTP and vdccLTP, as shown by the reduction of LTP in the presence of the VDCC-blocker nifedipine (Cavus and Teyler, 1996). Interactions between the kinase cascades involved in both types of LTP are likely.

Aging caused deficits in nmdaLTP, but increased the magnitude of vdccLTP (Shankar et al., 1998). Therefore, the previously reported lack of effect of aging on LTP may be due to compensation of opposite effects on nmdaLTP and vdccLTP. When lower intensity stimuli were used, little or no vdccLTP was induced, while nmdaLTP deficits were unmasked (Deupree et al., 1993; Moore et al., 1993). In summary, the data seem to indicate that aging shifts synaptic plasticity from a NMDA receptor-dependence to VDCC-dependence. However,

the issue is further complicated by selective age-related synapse loss and is not clear yet (Rosenzweig and Barnes, 2003).

Aging deficits in reactive synaptogenesis

Turnover of synapses was inferred from the simultaneous observation, in the same animal, of structures that imply synapse renewal (degenerating axons, growth cones and vacated postsynaptic densities). Electrophysiological and anatomical studies, such as those described by Hatton (1985) or Tsukahara (1985), could help to detect synapse renewal in living animals. Because of the technical difficulties to demonstrate spontaneous CNS synapse renewal in mammals, research on its cellular and molecular mechanisms have used systems where renewal is initiated experimentally by lesions. Synapse formation evoked by stimuli that are not part of the developmental program, e.g. lesions, is called *reactive synaptogenesis*. This process has been carefully studied in the rodent hippocampal formation (reviewed by: Nieto-Sampedro and Cotman, 1985; Collazos-Castro and Nieto-Sampedro, 2002).

Unilateral destruction of the enthorrinal cortex (enthorrinal cortex lesion, ECL) cause the loss of 90% of the synapses in the dentate gyrus outer molecular layer ipsilateral to the lesión. This massive deaferentation is followed by the restitution of lost synapses that leads to a reorganization of hippocampal circuits both ipsilateral and contralateral a the lesion. The laminar distribution of dentate gyrus afferents facilitates the analysis of axonal growth and synapse formation after lesions. Approximately 85% of the synapses lost after unilateral ECL are restored by sprouts from undamaged afferents. Homotypic and heterotypic systems contribute to synapse replacement (Cotman and Nadler, 1978; Steward, 1991; Deller and Frotscher, 1997), suggesting unspecific activation of pre-synaptic growth. The best characterized response to dentate gyrus deafferentation is the homotypic sprouting of temporodentate axons after unilateral ECL. The cell bodies of the neurons giving rise to the sprouts are located mainly in layer II of the contralateral EC. Initial studies suggested that collaterals from these neurons grew a relatively long distance thorough the midline to reach the deafferented dentate gyrus. Although this possibility has not been completely ruled out, now it is accepted that axons sprouting are already present in the contralateral dentate gyrus at the time of deafferentation, growing only inside the outer molecular layer (Steward, 1991; Deller and Frotscher, 1997). The number of synapses formed by these fibers increased 128-fold. Several types of presynaptic growth were observed here, including axonal branching, tangle formation, short axonal extension, terminal hypertrophy and multiple synapse formation.

Reactive synaptogenesis begins, in the young adult, 3 or 4 days postlesion, when the first axonal sprouts are detected, reaches maximal rate between 15 and 20 days and it does not conclude until two or three a tres months later. The process of clearing of debris after a lesion is much slower in aged than adult animals (Vijayan and Cotman, 1983), which delays sprout initiation. The synapse renewal mechanisms that operate in adult and aged animals are essentially the same that acted during development. However, during development

the net number of synapses increases, whereas renewal is the predominant process in the adult and synapse loss may occur in old age.

Disconnection of existing synapses during adult synapse renewal is formally analogous to developmental synapse elimination. Two disconnection processes, at least, occur in the adult and aged: presynaptic terminal degeneration, a slow process the intermediate stages of which can be observed microscopically and a second process, much faster (takes at most a few hours) and reversible, that occurs without presynaptic degeneration. In the second process glial cells interpose fine pseudopods between the pre- and post-synaptic elements. Synapse disconnection by the latter mechanism ressembles the physiological control of hypothalamic hormone secretion (Hatton, 1985), or the loss of afferents by axotomized neurons (refs. in Cotman et al., 1981). Synaptic activity and vdccLTP are associated to considerable variations in intraneuronal Ca^{2+} concentration, which also controls the polymerization state of microtubules and actin neurofilaments and, hence, spontaneous terminal degeneration, Ca^{2+}-wave propagation and astrocyte recruitment. These are some of normal brain aging effects on synaptic activity and half-life of nerve endings. Normal brain aging is associated with subtle morphological and functional alterations, rather than with obvious loss of neurons (Morrison and Hof, 1997). Several common features of aging CNS, observed in diverse mammalian species, include pyramidal neuron dendritic regression, synaptic atrophy, decrease of striatal dopamine receptors, accumulation of fluorescent pigments, cytoskeletal abnormalities and reactive astrocytosis and microgliosis (Finch and Roth, 1999). Age-associated deficits in particular neuronal circuits have been reported, yet the molecular basis of brain aging remains obscure. Among the various causal mechanisms postulated we may list instability of nuclear and mitochondrial genomes leading to alterations in gene expression, production of reactive oxygen species (ROS) that damage crucial targets, neuroendocrine disfunction associated with exposure to corticosteroids (Sapolsky, 1999) and altered calcium metabolism. In both, rodents and humans, glia activation occurs in normal brain aging, with considerable differences among different brain regions (Morgan et al., 1999). Activated microglia produce several pro-inflammatory mediators, including cytokines (IL-1, IL-6, TNF α), cytotoxic complement components, ROS, NO and excitotoxins like quinolinic acid (Akiyama et al., 2000). The hypothesis that induction of neuroinflamatory cascades is involved in age-related neurodegenerative disorders is now widely accepted.

Axon sprouting and growth factors: age effects

The formation of new neuronal contacts involves the growth of axons and/or dendrites and the differentiation of the structures characteristic of mature synapses. The formation of axon sprouts has two essential requirements: the presence of the specific *growth factors* and the existence of an appropriate substrate for the adhesion and growth of the new fibres.

Three classes of instructive factors are important for adult synapse renewal: i) *neuritogenic* factors, that cause neurite differentiation; ii) chemiotactic or chemiotropic factors, that direct the orientation of neurite growth; iii) factors

that control neurotransmitter choice, important for synapse maturation. Some growth factors exhibit more than one of these activities. Thus, NGF is neurotrophic for sympathetic neurons, for some sensory neurons and for CNS cholinergic neurons. For sympathetic neurons, NGF is also neuritogenic and chemiotactic. Laminin, a high molecular weight basal membrane protein, is capable, alone or associated to a heparan-sulfate proteoglycan, of initiating neurite growth, both during development and after a lesion. Furthermore, in the case of sensory neurons, NGF associated to laminin has higher neurotrophic and neuritogenic activities than the factor alone. Neuritogenic and neurotrophic activities are connected: intercellular adhesion proteins with neuritogenic activity act through a common domain with the tyrosin-kinase of fibroblast growth factor (Williams et al., 1994; Doherty et al., 1995). The general molecular features of neurotrophic factor mode of action are known (Russell, 1995). Binding of a factor to its receptor, a tyrosin-kinase, initiates a sequence that begins with the activation of the tyrosin-kinase, followed by a protein phosphorylation cascade that finally affects Ca^{2+} homeostasis (Cheng and Mattson, 1991; Schulman, 1995). Intracellular Ca^{2+} levels affect multiple fundamental neural processes (Simpson et al., 1995) and is the meeting point of nerve ending degeneration, LTP (Malenka, 1995), neurite initiation and growth, and cytoskeletal polymerization and organization (Mattson, 1988; Hoffman, 1995). Physiological levels of neuronal activity induce the production of neurotrophic factors and treatment with physiological levels of neurotrophic factors increases synaptic efficiency. Many effects of trophic factors depend on the synergy of at least two of them.

The two major sources of growth factors are the post-synaptic targets and glial cells. Innervation and activity regulate the post-synaptic target production of factors, decaying when inervation is complete and increasing after partial or total denervation. This observation explains in part why in the CNS axonal sprouts grow only short distances and why, when longer distance growth outside the CNS is induced, upon entering the CNS the terminals do not form synapses profoundly in the CNS tissue. Local axon sprouts quickly repopulate vacant postsynaptic sites after a lesion, arresting growth factor production by deafferented cells. The other major contributor to growth factor production is glia (Longo and Penhoet, 1974; Nieto-Sampedro et al., 1983; Rudge, 1993). The lesion by aspiration of the EC, filling the wound cavity with a gelfoam sponge, permitted to compare, in the same experiment but separately, production of secreted, diffusible and tissue-bound, high molecular weight neurotrophic (NTF) and neuritogenic activities. The temporal course of increase of growth factor activity in the hippocampus after enthorinal cortex lesion, correlated closely with the time-course of gliosis in that structure and with the cinetics of comissural fibre sprouting (Nieto-Sampedro, 1988a). The diffusible CNTF activity that collected in the Gelfoam filling the wound cavity was similar to the activity detected in extracts of the tissue that formed the walls of the wound (Fig. 2). The time-course of trophic activity accumulation in the Gelfoam was similar to production in the tissue, but with a time delay. The delay was very short in neonates, but considerable in adults and aged. The tissue CNTF activity observed in aged animals was similar or slightly higher than that in adults, but it did not diffuse to the Gelfoam. The molecule carrying the

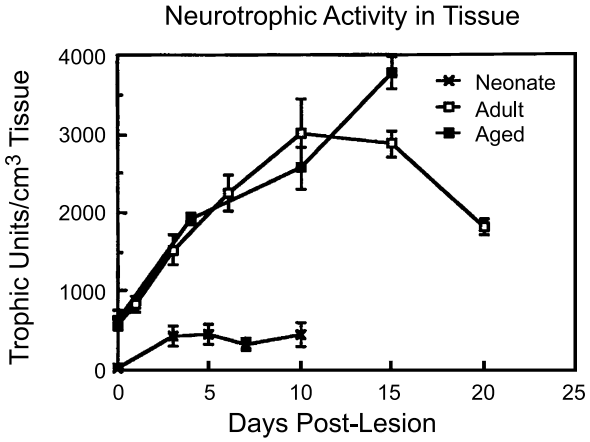

Fig. 2. The time-course of neurotrophic factor production by entorhinal cortex tissue in response to injury was strongly age-dependent and correlated, with a dependent delay, with non-neuronal cell number in the walls of the cavity

NTF activity in aged animals trophic for ciliary neurons, either had a molecular nature different from CNTF or was tightly bound to the tissue. Adult and aged animals expressed NTF activity like neonates, but probably embodied in different molecules. Regarding the neurite promoting activity, two molecular types were observed: a small diffusible Ca^{2+}-binding protein of the S100b family (Kligman, 1982), with sulfydryl groups in the active site and a large, extracellular matrix, poly-ornithine-bindable neurite promoting factor, PNPF. Entorhinal cortex lesions induced the enhanced production of S100b type in neonates and adults, but not in aged animals, which appeared to show no response or very limited response to injury (Needels et al., 1986).

The astrocyte surface, regulator of axonal growth, changes with age

Astrocytes, probably the most characteristic cell components of the glial scar, are probably the most plastic CNS cells, capable of changing in number and morphology in response to perturbations. Neuronal death or atrophy after a lesion or aging causes astrocytes to change shape, becoming ''reactive'' or ''fibrous''. The meaning of the word ''reactive'' referred to astrocytes is by no means precise. Most researchers take for granted that reactive indicates cells bigger that normal or ''resting'' astrocytes (Fig. 3A). Reactive astrocytes show a great increase in intermediate filament expression, which gives them the ''fibrous'' appearance of their alternate name. Astrocyte intermediate filaments are recognized by antibodies against glial fibrillation acidic protein (GFAP; Bignami and Dahl, 1974), the most characteristic marker of reactive astrocytes. The so-called glial scar formed in a CNS open lesion, essentially consists of a meshwork of *hypertrophic fibrous astrocytes* (Fig. 3B) over the lesion surface, overlayed by fibroblasts from adjacent connective tissue and collagen. Glial scar formation may represent the CNS attempt to isolate itself from

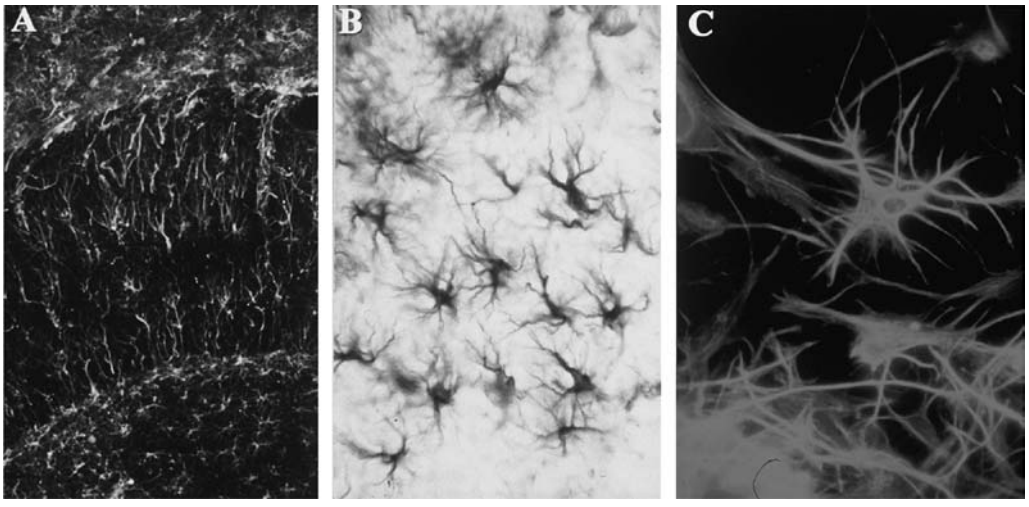

Fig. 3. **A** Resting astrocytes in the molecular layer of the dentate gyrus of an adult rat changed after injury to **B** hypertrophic fibrous reactive astrocytes and **C** reactive astroblasts

uncontrolled influences, reconstituting a new *glia limitans* but, it is also the major obstacle to the restitution of damaged connections. Again, astrocytes show simultaneously beneficial and deleterious roles where survival (restitution of a glial boundary) is in conflict with restoration of lost functions. It will be interesting to test whether inhibition of glial scar formation may lead to functional restoration without affecting survival.

Astrocyte number remains stationary in the adult, although they are able to divide in response to neuronal death or damage. Astrocytes proliferating in the adult mammalian CNS may be either mature astrocytes that have undergone dedifferentiation, remaining astrocyte precursors, new astroblasts arising from stem cells, or all these possibilities. The problem is clearly set, but its definite answer needs further research. Viable astrocytes cannot be cultured from adult mammalian CNS, unless the cultured tissue is adjacent to an injury site (Lindsay et al., 1982; Lindsay, 1986; Nieto-Sampedro, unpublished), when the astrocytes that proliferate have morphology and immunological properties similar to those of type 1 neonatal brain astroblasts (Fig. 3C; Lindsay et al., 1982; Lindsay, 1986). Part of the astrocytes dividing after brain or spinal cord injury definitely arise from stem cells (Holmin et al., 1997; Johansson et al., 1999) attracted to damaged tissue (Johansson et al., 1999; Helmuth, 2000). Astroblasts promote neuritogenesis, are a preferred substrate for neurite extension (Noble et al., 1984; Fallon, 1985; Pixley et al., 1987; Tommaselli et al., 1988) and during development often are seen associated to growth cones *in vivo* (Silver, 1984; Bovolenta and Mason, 1987). In contrast, the membranes of fibrous reactive astrocytes induced by Wallerian degeneration or toxin injection contain proteoglycans that cause growth cone collapse, inhibit neurite outgrowth and repel growing neuritis (Bovolenta et al., 1991a, b, 1992, 1993, 1997). The ratio of fibrous astrocytes to astroblasts possibly determines the overall neurite promoting or neurite inhibiting properties of the gliotic tissue

(Nieto-Sampedro, 1999). This ratio changes with age and gliotic tissue properties change with it. Aging increased the proportion of fibrous astrocytes in the Rhesus monkey's optic nerve (Sandell and Peters, 2002).

Aldynoglia, plastic CNS macroglia that promotes neuronal plasticity

Two of the few sites of the mammalian CNS where injured axons regenerate spontaneously are the hypothalamic-neurohypophyseal system and the olfactory bulb. Regeneration is possible in these loci because axons are associated to a type of growth-promoting macroglia, similar to peripheral Schwann cells, that we have called aldynoglia. These glial cells include ensheathing glia in the olfactory bulb (ECs), tanycytes (tan) in the hypothalamus and pituicytes (pit) in the neurohypophysis. Aldynoglia can be cultured and its growth properties, specific surface markers and interaction with diverse axonal typeshave been characterized (Gudiño-Cabrera and Nieto-Sampedro, 1996, 1999, 2000). The properties of aldynoglia present similarities and differences with those of CNS macroglia precursors. Their inmunophenotypes (Table 1) are similar to those of the O4-positive pro-oligodendrocytes that persist in the adult (Reynolds and Hardy, 1997). However, considering together their proliferation properties, growth promoting properties, interaction with neurons and immunological markers, the greatest similarity is with Schwann cells. Like Schwann cells, they show S-100b protein and p75-NGF receptor immunoreactivity, in contrast to astrocytes but in common with Schwann cells (Assouline and Pantazis, 1989;

Table 1. Immunological markers of central macroglia, aldynoglia and Schwann cells

Cell type	O4	p75	S100	ER	Vim	GFAP
Ast.†	−	−	+	−	−	++
Olig†	++	−	±	−	−	−
SC*	+	++	++	++	++	++
Tan†	+	+	++	++	++	++
Tan*	+	++	++	+	++	+
Pit†	+	+	++	++	++	++
Pit*	+	++	++	+	++	+
ECs†	+	+	++	+	++	++
ECs*	+	++	++	+	++	+

Cell immunoreactivity was: (++), very intense; (+), clearly positive; (−) negative. Reaction with the immunological markers indicated was examined: † in adult tissue *in situ*; * in cultures prepared from adult tissue. Astrocytes (Ast.), oligodendrocytes (Olig) and cultured non-myelinating Schwann cells (SC), were used as standards of immunostaining intensity, under the same experimental conditions as the rest of the cell types. *Tan* tanycytes; *Pit* pituicytes; *ECs* olfactory ensheathing cells. *O4* seminolipid, sulfatide antigen; *p75* low affinity NGF receptor; *S100* Ca^{2+}-binding protein S100; *ER* estrogen receptor-α; *Vim* vimentin; *GFAP* glial fibrillary acidic protein (polyclonal IgG). Immunostaining of tissue sections with polyclonal anti-S100 was not selective, i.e. weak staining of every type of glial cell was superimposed over intense EC or tanycyte staining

Ramón-Cueto and Nieto-Sampedro, 1992). Aldynoglia present the sulfatide and seminolipid antigens recognized by monoclonal O4 (Barnett et al., 1993; Gudiño-Cabrera and Nieto-Sampedro, 2000) in contrast to astrocytes, but in common with cells of oligodendrocytic lineage (Sommer and Schachner, 1981) and Schwann cells (Schachner et al., 1981). Other physiological properties of aldynoglia, such as their ability to reversibly enfold non-myelinated axons (Barres, 1992; Hatton, 1985; Theodosis et al., 1998), and its growth-promoting properties (Martini, 1994; Monti-Graziadei and Graziadei, 1979; Kafitz and Greer, 1999; Sonigra et al., 1999; Dellmann et al., 1987; Dellman and Carithers, 1993; Chauvet et al., 1995, 1996, 1998) are also reminiscent of non-myelinating Schwann cells. Aldynoglia transplants rejuvenate the CNS, e.g. promote CNS fiber repair after CNS lesions (Nieto-Sampedro and Ramón-Cueto, 1993; Ramón-Cueto and Nieto-Sampedro, 1994; Li et al., 1997, 2003; Pascual et al., 1997, 2002; Imaizumi et al., 1998; Navarro et al., 1998, 1999).

Schwann cells and aldynoglia show common features typical of developmentally immature cells, such as their ability to survive and divide in culture, an immature cytoskeleton (Pixley et al., 1984), markers of motility (polysialylated-neural cell adhesion molecule, PSA-NCAM; Wang et al., 1994; Hu et al., 1996) and migration (p75 NGF receptor; Anton et al., 1994; Carter et al., 1996; Franceschini and Barnett, 1996; Bonfanti et al., 1992; Theodosis et al., 1991). PSA-NCAM, absent or very low in mature astrocytes, is abundantly expressed throughout adulthood by aldynoglia. A similar situation is found with the of α-estrogen receptor, expressed on the surface of aldynoglia (Gudiño-Cabrera and Nieto-Sampedro, 2000) and Schwann cells (Jung-Testas et al., 1993) but absent from mature and hypertrophic reactive astrocytes.

Co-expression of ERα and p75 NTR participate in endocrine regulation, particularly that of estrogen (Gudiño-Cabrera and Nieto-Sampedro, 1999). ER are transcription factors and NGF/p75 signalling involves activation of NF-κB (Carter et al., 1996). Although p75 NTR activation by NGF is generally associated to apoptosis, NF-κB is a master switch that regulates the expression of many genes, some of which suppress apoptosis (Van Antwerp et al., 1996) and promote long-term survival (Carter and Lewin, 1997). Estrogen is also known to inhibit apoptosis (Thompson, 1995). Concomitant expression of ERα and NF-κB by aldynoglia possibly confer them the observed immaturity features and ability to enter the cell division cycle. Another hypothetical way in which signals from mitogens, estrogen and neurotrophins may be integrated, is through the CREB binding protein or CBP (Arany et al., 1994; Montminy, 1997). By integrating NGF and estrogen signals through ER and p75 NTR in Schwann cells (Carter et al., 1996) and in Schwann-like cells expressing ER and p75NTR, CBP may regulate the coordinated transcription of many genes leading to expression of the Schwann-like glial phenotype. Aldynoglia transplants in the injured spinal cord caused astrocyte reactivity to diminish or disappear (Verdú et al., 2001), a modification of the CNS environment that could also occur in the aging brain.

The ramifications of endocrine and neural senescence converge in the function of hippocampal glutamatergic synapses. Estradiol, by activating MAP

kinases enhances tyrosine phosphorylation of NR2 subunit of the NMDA receptor, which inhibits its proteolysis by calpain. Interactions between ERα and NMDA receptors may be uncoupled by aging, estrogen helping to retain a youthful synaptic phenotype (Adams and Morrison, 2003). An intracellular signalling cascade, involving Src, ERK2, ras-like proteins and the MEK pathway, stimulated by estrogen may be altered in old age (Bi et al., 2003) with deletereous effects on the translation-dependent phase of LTP and memory (Kelleher et al., 2004).

Posture and movement: effects of aging

Muscle contraction and its consequence, movement, underlay all human interactions. Thanks to the coordinated action of different muscles it is possible to talk, write, walk or use tools. Many visceral functions are possible also because the contraction or relaxation of muscles. Both posture and movement are strongly age-dependent.

Movements may be classified according to the neural system that induces them. *Reflex movements* are the most elementary form of motor behavior: a sensory signal triggers motor neuron activity, allowing stereotyped, survival-effective acts. Many control systems have been implemented over these basic sensorimotor systems, allowing a greater behavioral range that facilitates appropriate responses in a complex environment. *Voluntary movements* are induced by signals arising from integration and control systems, such as the neocortex and the basal ganglia. *Automatic movements* are stereotyped motor behaviour, intermediate between reflex and voluntary movements. Locomotion represents very well these stereotyped movements the execution of which may be induced by either brain control centres or by peripheral sensory signals. Control systems confer automatic movements *behavioral significance*. The kinetic chains performed during walking and produced by activation of neuronal networks organized in the spinal cord, generate the patterns required for the coordinated activation of the muscles involved. The activity of such networks, controlled by sensory information, by the cerebellum and by brainstem nuclei, in turn, controlled by neocortex and basal ganglia is affected by aging. *Behaviourally significant locomotion* needs (Grillner and Wallén, 1985): i) a signal to initiate the march, i.e. to assume the adequate posture and begin walking; ii) patterns of activation that generate the movement synergies, i.e. coordinated flexion and extension of the limb joints that produce body displacement; iii) a postural control capable of maintaining balance during displacement, which implies controlling the position of the centre of gravity while one or more limbs are in the air and generate enough anti-gravity force with the standing limbs to maintain body height; iv) the adaptation of the march to the organism objectives. In the aged, muscle unloading, a form of subtotal disuse, affects neuromuscular junction synaptic vesicles and endplate macromolecules (Deschenes and Wilson, 2003). The complexity of movement requires kinematic analysis combined with kinetic analysis and electromyography to have precise information on motor function changes with aging, and what effect therapies have on the various movement components.

Conclusions and perspectives

It is generally accepted that the processes of LTP induction and maintenance are the cell biological substrates of learning and memory. Axon sprouting and dendritic spinogenesis may be its morphological correlates. As with LTP, there are two different phases in spine formation, spine emergence and spine maintenance. As we age, it becomes more difficult to store, stabilize and retrieve memories and the memory traces decay more easily. Presynaptic terminal and neuronal activity is important for spine pruning and maintenance and neuronal activity can have a vast influence on the final number of spines. Aging may interfere with neural plasticity processes in a number of ways and at various levels with glial cells playing a fundamental role.

Aldynoglia, probably the most hopeful CNS lesion repair tool developed in the last two decades, is capable of both normalizing hypertrophic reactive astrocytes when transplanted to a region of heavy gliosis, and of producing a variety of neurotrophic factors that like BDNF have clear effects on LTP and terminal sprouting. Aldynoglia transplantation or generation from neural stem cells may be a valid strategy for aged CNS rejuvenation, with the limitation of aldynoglia's sensitivity to free radicals. Treatments that combine aldynoglia transplantation with exogenous supply of neurotrophic factors, free-radical destroying molecules and blocking antibodies to growth inhibitory proteoglycans may ameliorate pathological aging.

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