Eur Biophys J (1994) 23:79–93

European Biophysics Journal

Cytoskeletal involvement in neuronal learning: a review

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Received: 21 May 1993 · Accepted in revised form: 21 December 1993

Abstract. This paper introduces the ideas of neural networks in the context of currently recognized cellular structures within neurons. Neural network models and paradigms require adaptation of synapses for learning to occur in the network. Some models of learning paradigms require information to move from axon to dendrite. This motivated us to examine the possibility of intracellular signaling to mediate such signals. The cytoskeleton forms a substrate for intracellular signaling via material transport and other putative mechanisms. Furthermore, many experimental results suggest a link between the cytoskeleton and cognitive processing. In this paper we review research on intracellular signaling in the context of neural network learning.

Key words: Neural network · Cytoskeleton · Synaptic adaptation

1. Introduction

A fundamental challenge of current research is to explain the possible mechanisms for learning and cognitive processing in the brain. Such an explanation will entail concepts at multiple levels: the systems level (network of neurons), the neuron level (processing and adaptation of the neuron and its synapses), and the molecular level (synaptic and intracellular proteins and trafficking). Results from systems modeling of neural networks show us effective and important aspects for the individual neurons or processing elements that enable the neural networks to learn to recognize patterns. Biophysical mechanisms for these functional capabilities can then be examined at the level of protein molecules.

Neural network learning paradigms, a focus of recent attention, show how networks of neuron-like components can learn through adapting synaptic strengths. Learning is done in response to patterns that stimulate the network, which learns to classify those patterns. Powerful learning capabilities have been discovered for neural network paradigms such as back propagation, counter propagation, sigma-pi networks, time-delay neural networks, adaptive resonance theory (ART), and networks with competitive layers. Many of these paradigms require reciprocal communications between pairs of neuron-like components and require information flow to go backwards through the network as well as forwards. But real neurons have membrane mediated signaling that travels in the "forwards" direction – dendrite to axon terminus – as post-synaptic potentials signal from dendrites to the spike initiation zone and action potentials travel down axons, away from the soma. Two-way communication could occur by nerve impulses but world require pairs of neurons to synapse onto each others dendrites, at sites already receiving synapses from other neurons. This regular and intricate arrangement has not been observed. Reciprocal communication could more plausibly be mediated by intracellular signals going in the reverse direction, with the neuronal cytoskeleton mediating such intracellular signals. This arrangement requires anatomical structures that are readily observed.

In this paper we introduce the ideas of neural networks in the context of cytoskeletal structures within neurons and the role such structures could play with respect to intracellular signaling. We review the neural network approach, in which synaptic strengths are adapted to produce learning in the network. We identify specific neural network learning paradigms that would require "backwards" propagation of signals – axon to dendrite – and other intracellular signals. The structure of the neuronal-cytoskeleton is then described with emphasis on candidate mechanisms for supporting intracellular signals. Although one mechanism, material transport, has been verified by extensive experimentation, such transport is relatively slow. Faster mechanisms would enable learning to take place more quickly. Thus we summarize additional mechanisms for faster signaling along the cytoskeleton

Abbreviations: MT, microtubule; MTs, microtubules; ART, adaptive resonance theory; RCE, restricted coulomb energy; MAP, microtubule associated protein; NO, nitric oxide

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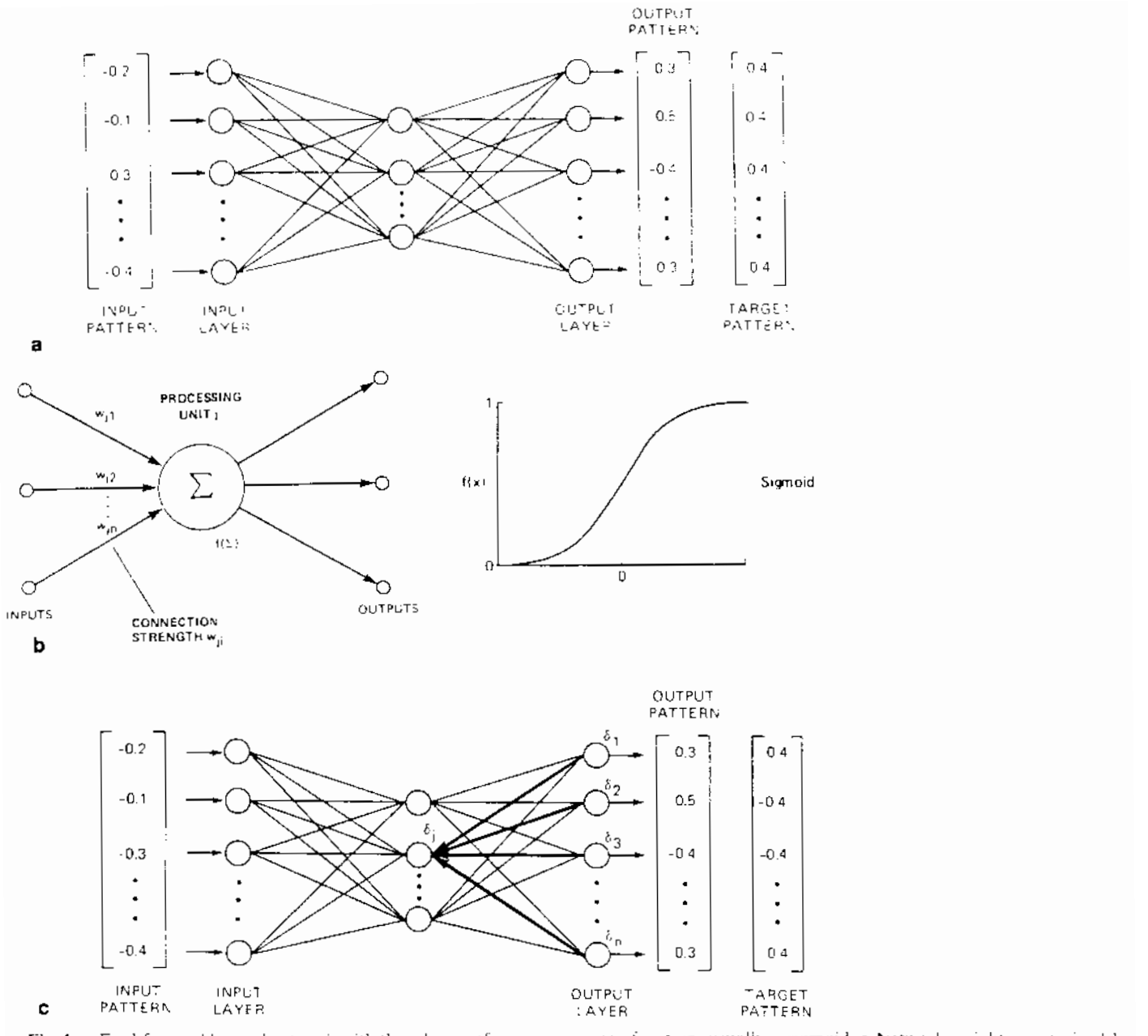

Fig. 1. a Feed-forward layered network with three layers of processing units: input, hidden, and output layers. Each layer is fully interconnected to the next layer in a forwards direction. A weight is associated with each interconnection and an activation level is associated with each processing unit. **b** Individual processing units perform a weighted sum of arriving inputs and then compute a squashing function, usually a sigmoid. **c** Network weights are trained by back-error propagation in which error delta values for each unit are computed and used to correct incoming weights. Target vectors are the source for the error delta value computations. Reprinted from Dayhoff (1990) with permission

Weights associated with interconnections that go to the output layer are changed as follows:

$$\Delta w_{ji,k-1} = \eta \delta_{j,k} a_{i,k-1} \tag{4}$$

where η is the learning rate parameter. Although the weight adjustment in (4) is specified precisely in a mathematical equation, approximations will suffice. For example, quantized increments or decrements in weights are sufficient for learning; later iterations can compensate for non-optimal weights, as training is completed. Also, the value of η can be raised or lowered during training; usually lowering η slowly provides better learning.

The above description assumes a layered and fully interconnected network, but the back-propagation learning paradigm applies to more irregular configurations, with interconnections skipping layers, going to lower layers, and sparse interconnections. Figure 2 depicts a layered fully connected network in a biological context.

Error-differencing can take place between the output signal of the neural network and an external signal indicating the target value. If each signal is coded by its firing

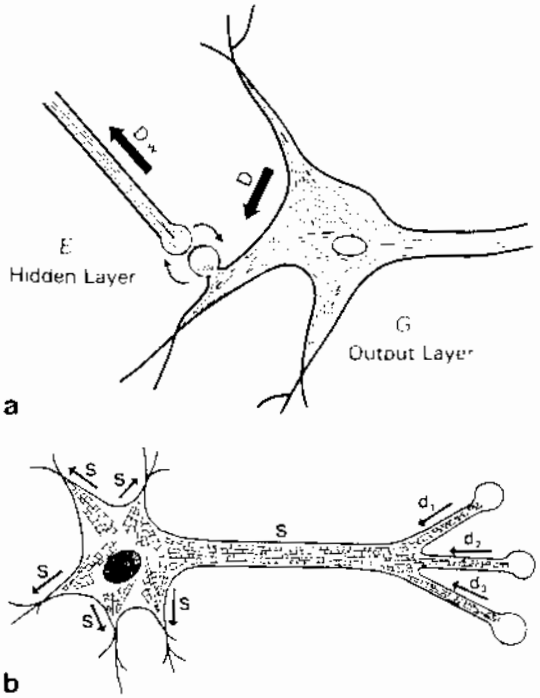

Fig. 4. **a** If the network has more than two layers of neurons, then error feedback signals would need to be carried backwards across synapses via a reverse transmitter (e.g., NO) **b** Internal signals traveling up axons would be merged at the axonal trunk, resulting in a summation of signal intensity. Reprinted from Dayhoff et al. (1993)

error signals through the network and could be considered variations of the original back propagation paradigm. For example, the sigma-pi network multiplies groups of incoming signals before a summation is done at the target processing unit (Rumelhart et al. 1986). Errors are then back propagated through the network to correct the weights.

The time-delay neural network (TDNN) propagates error backwards to adjust weights in spite of time delays along interconnections, and the ATNN back-propagates error correction signals that are used to adapt time delays along interconnections (Waibel et al. 1989; Day and Davenport 1993; Lin et al. 1992). These paradigms allow for learning of spatiotemporal patterns.

Recurrent networks allow for lateral and backwards interconnections in the network and adapt weights along all interconnections; the connections may be arbitrarily placed (Werbos 1988). Back propagation itself does not have to adhere to a fully-connected layered topology but can also have arbitrarily placed forwards connections. These networks all depend on the backwards flow of information (about errors) through the network, the construct that requires axon-to-dendrite signaling biologically.

Other learning paradigms have powerful functional approximation and pattern mapping capabilities. The work of Copper and coworkers on the RCE networks includes schemes for recruiting hidden units as needed by an externally connected layer of output units (Reilly et al. 1982). Thresholds of hidden units are adjusted according to information sent backwards from the output layer; this information depends on error differences. These networks map input patterns to desired output patterns. This also requires reverse intracellular signaling, possibly mediated by the cytoskeleton in biological systems. In this case, however, the signal may only have to propagate backwards along the axon to the cell body where the threshold is set.

An important class of neural network architectures consists of two layers of bidirectionally connected cells. The most notable of these architectures is ART (adaptive resonance theory) (Carpenter and Grossberg 1987, 1988). The top-down and bottom-up weights have separate rules for adjustment during learning. Recognition of incoming patterns occurs with "resonance", a state in which activation flowing downwards reinforces that flowing upwards. Since each unit in the bottom layer is bidirectionally connected to each unit in the top layer, the obvious biological analog is forwards signaling along axonal membranes and backwards signaling intracellularly along the cytoskeleton (Dayhoff et al. 1992c).

Other researchers have proposed learning mechanisms that employ communication between dendritic sites. Heterosynaptic mechanisms proposed (Finkel et al. 1989) utilize a selectionist population approach in which other dendrites on the same neuron communicate to modify a given dendritic synapse. Pribram (1991) has proposed dendritic influences acting as a field effect and having mechanisms of communication other than that channeled along membranes.

3. The neuronal cytoskeleton

The cytoskeleton, a lattice-like network of protein polymers and associated proteins, is found in the interior of neurons and collectively supports the cell structure and internal cell processes. This network includes microtubules (MT), centrioles, actin filaments and neurofilaments, membrane anchoring proteins, and microtubule associated proteins (MAPs) that crosslink MTs and other structures. Microtubules and other cytoskeletal components are found in virtually all eukaryotic cells, and provide physical and structural support to the cell (see Fig. 5). In addition, microtubules provide a communication and transport channel between remote cell parts. In most cells, the MTs connect the cell center (centriole) to the cell periphery in a radial pattern. In nerve cells, MTs have evolved a striking adaptation in that the microtubular lattice extends into the extremities of the axons and the dendrites, and some MTs may bypass the cell center. These internal highly ordered structures allow not only for the mechanical transport of material particles, but recent models have suggested that the cytoskeleton might be capable of transmitting fast signals and could do so internally within a nerve cell (Rasmussen et al. 1990). A variety of candidate mechanisms have been proposed for microtubule signal propagation, including propagating conformational changes and ionic motions (Hameroff 1987; Hameroff et al. 1989; Rasmussen et al. 1990).

Burns 1978). Similar patterns can be obtained by coherent phonon mode maxima calculated for MTs (Samsonovich et al. 1992), and coherent phonons have been proposed as a candidate mechanism for signaling along MTs. Some MAPs form bridges that laterally connect specific subunits on parallel-arrayed MTs to neurofilaments, membrane proteins, and organelles.

Dynein and kinesin are motor proteins that use biochemical energy from ATP hydrolysis for mechanical movement along MTs. These molecules bind to cell organelles and expend energy to cause the organelles to move along MTs like trains on a track (Allan et al. 1991). Similar movements can be caused in vitro with beads. Movement requires ATP as an energy source, hence dynein and kinesin can be considered motor proteins. The result is a form of material movement called axoplasmic transport or dendritoplasmic transport. Extensive experimental evidence exists for these motorized movements throughout the nerve cell. Material transport can be considered a mode of intracellular signaling in which information is represented by the presence, absence, or movement of particular substances.

Neurons are distinguished from other cells by their highly elongated processes (axons and dendrites) and must maintain their nutrient competence by a flow of material from regions near the soma to their elongated extremities. Since most cellular biosynthesis occurs in the region of the cell body, enzymes, receptors, neurotransmitters, and other substances must be transported. The transport of material away from the cell body towards axonal and dendritic extremities is called anterograde transport, whereas transport towards the soma is termed retrograde transport. Retrograde transport may recycle some material or provide feedback information. Axonal anterograde transport is generally classified by the rates at which transport of material occurs. There are different, distinct forms of fast anterograde transport with rates of 100–400 mm/day, 20–70 mm/day, and 3–20 mm/day (Vallee and Bloom 1991), but rates of 400–2000 mm/day have also been reported (Ochs 1982). They are, in all likelihood, mediated by different mechanisms and involve the transport of different material particles, possibly different sizes of polypeptides (Grafstein and Forman 1980). The two forms of slow anterograde transport have transport rates on the order of 0.1–4 mm/day and presumably involve movement of the cytoskeleton and its membrane connections (Brady and Lasek 1981). Our knowledge of retrograde material transport is not as extensive as anterograde transport although reputed rates are generally of the same of magnitude, about 300 mm/day (Grafstein and Forman 1980).

The polar nature of MTs noted previously offers directionality to the transport motor which somehow allows for the coupling and uncoupling of selective carrier proteins. Kinesin and cytoplasmic dynein proteins appear to have a role in fast anterograde and retrograde axonal transport respectively, whereas dynein has been implicated in slow transport. MTs also play a role in transporting material from the cell body to the dendritic terminals (Allan et al. 1991). Thus axonal retrograde transport and dendritic anterograde material transport allow for an efffective coupling between axon terminals and the dendrites.

Axonal and dendritic transport, important for synaptic maintenance and modulation, depend on motor proteins which hydrolyze ATP for energy. Transported materials bind to motor proteins kinesin, cytosplasmic dynein and/or dynamin which then, as a complex, interact transiently with the MT structure like trains on a track (Pfister et al. 1989; Brady et al. 1990). The movement consumes ATP hydrolysis energy in the process; however, the mechanism for orchestration and sequential signaling within MTs is unknown. Material can travel in opposite directions along a single microtubule, and can travel simultaneously, but particles carried by kinesin always move towards the + end and those carried by dynein move towards the − end.

Other cytoskeletal activities involve the molecular machinery of cell division, growth, differentiation, formation of synapses and dendritic spines (Burgoyne 1991; Hirokawa 1991). Formation of synapses, including dendritic spines, involves neurite and growth cone extension by polymerization of MT, actin, and other cytoskeletal proteins. Once established, synapses are maintained and modulated by axoplasmic transport and other mechanisms. In single cell organisms such as amoeba and paramecium, which do not have synapses or brains to explain their adaptive behaviors, relatively complex behaviors are controlled by or involve the cytoskeleton (Wichterman 1985; Hameroff et al. 1993).

Actin filaments are another major part of the cytoskeleton in addition to MTs. Actin filaments are polymerized actin strands that form their own lattice-like network throughout the cell. These filaments cross each other, and are interspersed with MT/MAP lattices and neurofilaments. They are more flexible than MTs, capable of more bending because tubules have some rigidity. Usually a dense lattice of actin is present. Actin strands can be seen in pre- and post-synaptic areas, but cover the cell as well.

Actin strands play an important role in the pre-synaptic nerve terminal, where they are the major cytoskeletal element (Hirokawa et al. 1989). Although arranged in a meshwork, actin filaments are mainly perpendicular to the membrane at the site of neurotransmitter release. Secretion of transmitter vesicles is accompanied by changes in the assembly and disassembly of actin filaments (Sontag et al. 1988). Blocking the disassembly or assembly of actin filaments changes the amounts of neutrotransmitter released in response to depolarization (Bamburg and Bernstein 1991). Actin disassembly is required for higher release and reassembly appears to cause more limited release.

Synapsin 1, present in pre-synaptic terminals, can bind to tubulin, actin, and synaptic vesicles, according to biochemical studies (Goldenring et al. 1986). Synapsin 1 crosslinks actin filaments to each other and to synaptic vesicles (Hirokawa et al. 1989). Cytoskeletal binding to synapsin 1 is reported modulated by phosphorylation of synapsin 1 via protein kinase II, dependent on Ca^{2+} calmodulin (Schiebler et al. 1986). Phosphorylation of synapsin 1 could regulate the release of neurotransmitter,

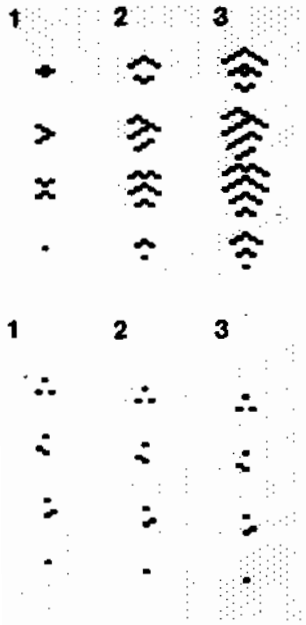

Fig. 7. MT pattern signaling, predicted by computations of MT automata models (Rasmussen et al. 1990). Black elements are tubulin dimers in the β conformation state; white elements are background α conformational states. *Top*: Three successive time frames for four object (gliders) moving downward, leaving "wakes" which result in traveling wave patterns. *Bottom*: Three successive time frames for a "dot glider" and three other gliders. Simulated with different automata threshold parameters. These gliders travel leftward without a wake. From Rasmussen et al. (1990) with permission

velocity of traveling membrane potentials. Thus cytoskeletal signals, if utilizing this mechanism, would propagate in concert with action potentials, in either direction.

Cellular automata are computational systems described by Von Neumann (1966). The idea of cellular automata models within neurons as a basis for intracellular signaling or information processing related to cognition was introduced by Conrad and coworkers (1973), who originated the term "molecular automata" for such models. Automata models require a lattice with subunits that can exist in two or more states at discrete time steps ("clocking frequency") governed by transition rules between states. Transition rules depend on neighboring subunits in the lattice. Depending on the pattern of initial states and transition rules, patterns can propagate ("gliders"), interact, compute and store information, often in exceedingly complex ways (Wolfram 1984 a, b). Von Neumann (1966) proved mathematically that cellular automata are capable of universal computation.

A model can be constructed in which tubulin has two conformational states, α and β. A signal can then be encoded as a "glider", a traveling cluster of one state on a background of the other state. For example, a positive polarity could be a signal in state β on a background of state α, and a negative polarity could be a signal in state α on a background of state β. In this case the size of the traveling cluster would represent the signal's magnitude. In an alternative mode, the signal could be a traveling cluster of (mostly) α states, on the background configuration of β, or vice versa. The percent density of α states could then represent the signal magnitude. There could be a "baseline" signal of size b so that a signal of size D is interpreted as D − b. This would allow the encoding of both negative and positive numbers by a signal that has only a magnitude. From models of learning in neural networks, it appears preferable for the internal signal to cary both a magnitude and polarity, although for many learning paradigms simply a binary signal of a magnitude alone would suffice.

Propagated conformational changes could occur on an extremely fast time scale, as proteins exhibit conformational alterations over a wide range of time scales, and very rapid (10^{-15} s) changes occur in protein side chains or local regions. Conformational transitions involving the protein globally generally occur in the nanosecond to 10 picosecond (10^{-11} s) range (Frauenfelder et al. 1988; Karplus and McCammon 1983). If tubulin were to have more than one stable conformational state, then these conformational states could store information, and if changes in state occurred then these changes could possibly process information. Many models that relate tubulin conformational states within MTs to possibilities for signaling and information processing have appeared in the literature. These models include propagating tubulin conformational changes mediating sensory transduction in ciliary MT (Atema 1973), conformational gradients among tubulin subunits (Roth and Pihlaja 1977), changes in MT-tubulin lattice symmetry (Koruga 1984), memory storage in neurofilaments (Barnett 1987) automata-behavior in MT (Hameroff et al. 1989; Rasmussen et al. 1990), and molecular computing (Lahoz-Beltra et al. 1993). Although most of these studies are theoretical or speculative, they open up a new approach towards understanding the potential impact of protein conformational changes.

Frohlich (1970, 1975, 1986) proposed that protein conformational states are coupled to charge redistributions such as dipole oscillations within specific regions of proteins. His model also predicted that proteins which have an interconnected lattice structure, are joined within a common voltage field, and are "pumped" with biochemical energy (e.g. protein phosphorylation, GTP or ATP hydrolysis) will display long-range coherent excitations in the range from 10^{-9} to 10^{-11} s. Such excitations may also be described as acousto-conformational transitions ("phonons") in the GHz to microwave frequency range. Experimental evidence for such coherent excitations includes observation of GHz-range phonon excitations in proteins (Genberg et al. 1991), sharp-resonant, nonthermal effects of microwave irradiation on living cells (Grundler and Keilman 1983), GHz induced activation of MT pinocytosis in rat brain (Neubauer et al. 1990) and long-range regularities in cytoskeletal structures, such as the super-lattice attachment pattern of MAPs on MT (Kim et al. 1986). A model that predicts MAP attachment sites is based on phonon excitations (Samsonovich et al. 1992).

Traveling waves that propagate without changing form and maintain localized shape are called "solitary waves". In special cases where they can pass through each

initiate MT signals. For example, protein kinase C (activated by membrane events, such as binding of NMDA and glutamate to receptors) phosphorylates MAP-2 in dendrites, and similar events could occur with other MAPs in axons.

3. *Calcium-initiated events.* Calcium is well-known to be released during synaptic activity, and is capable of binding to calmodulin. Since calmodulin is bound to MTs and MAPs, this coupling could in turn cause conformational or other changes in the MTs which initiate a signal up the MT. Calcium might also directly bind to MTs, initiating tubulin conformational changes.

4. *Binding.* If a specialized protein or molecule binds at the end of the MT, to a MAP, an anchoring protein, or to the MT itself, then binding could cause a conformational change that initiates a MT signal. Particular proteins might even be responsible for initiating different signal patterns. Furthermore, such a molecule might be a compound such as NO, that diffuses in a retrograde fashion across synapses, or another compound that is activated by such a retrograde messenger.

5. *Anchoring proteins.* Fodrin, anchorin, and other membrane-coupled proteins might initiate signals at the axonal end of a MT, because they are known to form bridges from the MTs to the synaptic membrane. In this case the signal might be initiated by the membrane potential, membrane proteins, second messengers, or other activity at the membrane, or by modulations in the distance between the membrane and the MT.

6. *Chemical messengers.* Other chemical messengers might interact with MTs, MAPs, or anchoring proteins to effect a signal initiation at the microtubular end. Ben Ze-ev (1991) reviews possibilities that involve a receptor bonding to an intermediary which in turn interacts with the cytoskeleton. An important chemical messenger to consider is a retrograde synaptic transmitter such as NO, that might initiate signals along cytoskeleton in the presynaptic area based on activity in the synaptic cleft or activity at the post-synaptic site.

5. Cognitive processes

Experimental evidence suggests that the cytoskeleton may be directly involved in neuronal information processing, cognition, and learning. For example, Mileusnic et al. (1980) correlated tubulin production and microtubule activities with peak learning in baby chickens. A study by Cronly-Dillon et al. (1974) on baby rats showed that at the beginning of their critical learning phase for the visual system (when the rats first open their eyes), neurons in the visual cortex begin producing vast quantities of tubulin. When the critical learning phase is over (when the rats are 35 days old), tubulin production is drastically reduced. Kudo et al. (1990) correlated the amount of reduction in MAP2 levels with the degree of cognitive impairment in gerbils exposed to cerebral ischemia (lack of brain blood flow). Bensimon and Chermat (1991) found that selective disruption of brain MTs by the drug colchicine caused cognitive defects in learning and memory which mimic the clinical symptoms of Alzheimer's disease. One of the neuronal MAPs is axon-specific "tau protein", the major constituent of the neuropathological correlate of Alzheimer's disease (Matsuyama and Jarvik 1989).

Conventional wisdom generally links cognitive functions including learning with synaptic plasticity, and evidence linking plasticity to the cytoskeleton includes the following. Lynch and Baudry (1987) have studied synaptic changes in hippocampal neurons. They have examined long-term potentiation (LTP) of synaptic efficacy in glutamate-NMDA hippocampal neurons, a correlative model of learning. They find, as does Friedrich (1990), that LTP depends on rearrangement of the subsynaptic cytoskeleton. Other studies have suggested that cytoskeletal proteins directly link to nerve membrane ion channels and receptors and that the intra-neuronal cytoskeleton is linked to nerve membrane excitability and synaptic transmission (Matsumoto and Sakai 1979; Hirokawa 1991).

Desmond and Levy (1988) have studied dendritic spine structural changes during a synaptic learning paradigm. They find mechanical shape changes in spines mediated by cytoskeletal actin connected to microtubules in dendrites. Kwak and Matus (1988) and Aoki and Siekevitz (1985) have shown that in neurons deprived of input, the cytoskeleton depolymerizes. The latter authors have also found that signaling and regulation for dendrite spine synapse function depends on phosphorylation of a cytoskeletal protein: the dendrite-specific MAP, called MAP-2.

Halpain and Greengard (1990) have shown that activation of glutamate-NMDA receptors induces rapid dephosphorylation of MAP-2. MAP-2 is responsible for the consumption of a significant portion of brain biochemical energy. MAP-2 phosphorylation and de-phosphorylation are regulated by cyclic AMP-dependent protein kinase and calcium-calmodulin protein kinase, second messenger systems activated by neurotransmitter-receptor binding. Theurkauf and Vallee (1983) have found MAP-2 to be the major substrate for endogenous cyclic AMP-dependent phosphorylation in cytosolic brain tissue, and they concluded that MAP-2 phosphorylation may be an important reaction in response to neurotransmitter stimulation. Schulman and Lou (1989) and Aszodi et al. (1991) have shown that membrane receptor initiated second messengers (e.g. Ca^{++}, cyclic AMP) converge on protein kinase A and/or Ca^{++}/calmodulin dependent protein kinases which respond by prolonged phosphorylation of intracellular proteins including MAPs, MTs and neurofilaments (Vallano et al. 1986). These authors suggest that such prolonged phosphorylation, which supplies biochemical energy, also participates in learning.

Bigot and Hunt (1990) showed that glutamate and NMDA stimulation of cultured neurons cause a redistribution of tau and MAP2. Other couplings between the cytoskeleton and membrane-synaptic function include second messenger systems such as G-proteins (Rasenick et al. 1990), calcium ion fluxes, and direct links via fodrin.

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