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A Unifying Hypothesis of Alzheimer's Disease. I. Ageing Sets the Stage

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In a series of five papers, evidence from neurobiology, endocrinology and immunology is integrated into a holistic, coherent hypothesis accommodating genetic, medical and environmental risk factors into a cascade of pathophysiological events that leads to the clinical manifestation of Alzheimer's disease (AD). The perturbation of the calcium-energy-oxidative stress triangle emerges as pathophysiological leitmotif of ageing and AD. Cellular Ca^{2+} homeostasis and energy metabolism are closely interdependent. Ca^{2+} ions regulate the activity of a variety of rate-limiting enzymes of the tricarboxylic acid cycle and respiratory chain. Under physiological circumstances, the supply of energy according to demand is regulated by Ca^{2+} cycling across mitochondrial membranes. In certain pathological conditions, Ca^{2+} uncouples electron transfer and oxidative phosphorylation and increases the mitochondrial production of oxygen radicals which in tandem with Ca^{2+} precipitate the breakdown of mitochondrial function and structure. As most important risk factor, ageing sets the stage for the development of AD. The delicate regulation of the neuroendocrine network which physiologically modulates the Ca^{2+}-energy-redox homeostasis, deteriorates in ageing, compromising the hormonal balance between neurotrophic/protective and neuroaggressive factors. Thus, levels and/or signal transduction pathways of neurotrophic-factors such as neuropeptide Y, neurotrophins, DHEA/DHEAS, gonadal hormones, melatonin, insulin, insulin-like growth factors, somatostatin, thyroid hormones, and substance P decay, paralleled by the compromise of the hypothalmic-pituitary-adrenal (HPA)-axis feedback inhibition leading to a hyperresponsiveness to stress and a loss of diurnal rhythm of secretion of neuroaggressive glucocorticoids. Both add up to disrupt Ca^{2+} and energy homeostasis, put the nerve cells under metabolic and oxidative stress and lead to a compromise of neuronal excitability, signal transduction processes and neuronal plasticity. Subject to the same endocrinological dysregulation, the ageing immune system exhibits a primitive response pattern with impairment of specific cellular and activation of unspecific humoral and microglial immune responses. Thus, the ageing-related concerted perturbation of the homeostatic control in the neuroendocrino-immunological network creates phenomena which in many aspects are qualitatively similar to changes in AD and lay the foundations for the development of the disease. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; ageing; calcium; energy metabolism; oxidative stress; mitochondria; corticosteroids; neuropeptide Y; DHEA; oestrogen; melatonin; insulin-like growth factors; insulin; somatostatin; thyroid hormones; nerve growth factors; substance P; immune system

INTRODUCTION

The aetiology of Alzheimer's disease (AD) is enigmatic. Much has been learned about the disease which was described first by Alois Alzheimer (1907) and which was named after him. Although our knowledge has increased enormously particularly in the last 15 years, the 'Alzheimer puzzle' has not been assembled yet. Some 30 000 papers, the result of the collective research of thousands of scientists, have been published in the last 30 years. Owing to the concomitant lack of a unifying concept and the rapid growth of the database, the situation appears increasingly inextricable. Many theories are amassed, others have already been classified, such as the amyloid cascade hypothesis (Hardy and Higgins, 1992), the cytokine cycle hypothesis (Griffin *et al.*, 1998), the calcium hypothesis (Kachaturian, 1984), the energy metabolism hypothesis (Beal, 1992; Hoyer, 1993), and free radical hypothesis (Volicer and Crino, 1990; Harman, 1993; Olanow, 1993), and the deleterious network hypothesis, integrating the latter three concepts (Ying, 1997a). The pathophysiological relevance of some of these theories is disputed (e.g.

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Neve and Robakis, 1998). However, the question remains as to how these concepts may be related to each other.

AGEING AND ALZHEIMER'S DISEASE

Ageing is the single most important risk factor for AD (Katzman, 1986). Even in genetically predisposed individuals, disease onset rarely occurs prior to age 45. In sporadic cases, both the prevalence and incidence rise approximately exponentially at least between ages 65 and 90, doubling every 5 years (reviewed by Katzman and Kawas, 1994; Jorm and Jolley, 1998). The debate is both controversial and unresolved if sporadic AD is characterized by some form of accelerated or pathological ageing (the intrinsic or ageing-related model), or if it represents a disease entity on its own which happens to run in parallel to normal ageing (the extrinsic or age-related model). This controversy will be discussed in depth in part IV of this series. The following first part of the series will provide abundant evidence that age is not the innocent bystander, the pacemaker, which only provides the chronological frame, which is needed to grow the plaques if x molecules Aβ aggregate per second, as was suggested in the β amyloid concept (Beyreuther *et al*., 1991). Ageing, understood as a biological process rather than a 'zeitgeber', provides at least the biological background which sets the stage on which the pathophysiological processes occur. To fully appreciate these processes, some recently recognized relationships between calcium, energy homeostasis and oxidative stress will be outlined first.

CALCIUM AND PHOSPHATES: YIN AND YANG

Evolution assigned Ca^{2+} a unique role as a stabilizer of connective tissue, transmitter of signals, and regulator of dynamic processes (Williams, 1992, 1996). At a procaryotic stage of evolution, phosphates dominate cellular signalling both linking information, material and energy transfers. At this stage Ca^{2+}, which was present in the environmental prebiotic 'soup' at high concentrations, had the status of a toxin which had to be eliminated from the cell to prevent cross-linking of anionic proteins, DNA and RNA. With the division of space in eukaryotic cells some 1·8 billion years ago, a messenger system was demanded, linking the cytoplasmic phosphates with both the energy supply (in form of energy-rich phosphates provided by incorporated organelles, i.e. mitochondria and chloroplasts) and genomic events. The physicochemical features of Ca^{2+}, its ability to diffuse and react very quickly, make it an ideal messenger ion. By virtue of its ionic characteristics which allow a very variable and hence flexible coordination number, Ca^{2+} is uniquely endowed to bind with an optimal kinetic and binding strength to all kinds of proteins, particularly kinases and phosphatases, effecting a reversible change of their conformation. The promotion from a poison to a messenger required the evolution of a homeostatic system. It had to be able to maintain a 'non-poisonous' Ca^{2+} concentration with the help of buffer systems such as Ca^{2+}-binding proteins and vesicles, e.g. the reticula as internal Ca^{2+} sources. Thus, a closely and intricately interrelated network of two messenger systems evolved (Williams, 1992, 1996), consisting of Ca^{2+} and phosphate compounds including cyclic AMP, inositol polyphosphates and guanine nucleotide-associated transduction systems (for recent reviews see Kasai and Petersen, 1994; Exton, 1996; Pacheco and Jope, 1996; Mons *et al*., 1998). This network, which relies on the interdependence of Ca^{2+} and energy homeostasis (see below), regulates the major dynamic events associated with life. On the other hand, a perturbation of this network, which overwhelms the homeostatic control, unleashes the toxic properties of Ca^{2+} and makes Ca^{2+} the destroyer of cellular function and, eventually, integrity, either through necrotic or apoptotic pathways (Mattson, 1992; Dubinsky, 1993; Nicotera and Orrenius, 1998). The molecular events along these pathways will be a leitmotif during the pathophysiological development of AD and therefore require some basic considerations.

NEURONAL ACTIVITY AND CALCIUM

This chapter can only give a rather global account of the different physiological neuronal functions of Ca^{2+}. For further reading, the reviews of Blaustein (1988), McBurney and Neering (1989), Mattson (1992), the special issues of Trends in Neurosciences volume 12 (1989) and Journal of Neurobiology volume 25 (1994) and the book by Kostyuk and Verkhratsky (1995) are recommended. As it has become obvious that energy and Ca^{2+} homeostasis of the nerve cell are intimately interwoven, reference will be made to the energetic consequences of the active Ca^{2+} turnover in this excitable tissue.

Ca^{2+} ions play a pivotal role in the neurons' function and integrity. In neurones at rest, there is an exceedingly high transmembranous Ca^{2+} gradient, the intracellular concentration being four orders of magnitude lower than the extracellular concentration. By maintaining the cytosolic free Ca^{2+} concentration in the order of 100 nM, the nerve cell provides the high signal to background ratio which is essential for the Ca^{2+} ion to serve as a second messenger. External signals such as neurotransmitters, hormones, growth factors, and action potentials — to name only the most important ones — modulate the influx of Ca^{2+} via a multitude of receptor- and voltage-gated Ca^{2+} channels and/or release of Ca^{2+} from internal stores. Moreover, other ion channels that help to shape the frequency and duration of electrical responses are modulated by Ca^{2+} either directly or indirectly through Ca^{2+}-controlled kinases and phosphatases. This temporally and spatially coded Ca^{2+}-regulated message affects virtually myriads of cellular systems controlling and mediating gene transcription, protein synthesis, axonal transport, secretion of neurotransmitters, synaptic contacts, growth and repair. Hence, literally all neuronal functions dealing with development, neuronal plasticity, regeneration and degeneration are controlled by Ca^{2+}.

Not surprisingly, given the paramount importance of this ion for functioning and survival, the cell has developed a whole variety of delicately tuned processes and structures which are instrumental in maintaining the homeostasis of Ca^{2+}. Once Ca^{2+} has entered the cell or has been released from internal stores and after delivering its signal, Ca^{2+} is instantaneously bound to a multitude of Ca^{2+}-binding proteins or secreted into cellular organelles such as the endoplasmic reticulum and the mitochondria. While these Ca^{2+}-buffering systems allow the short-term coping with Ca^{2+} loads, Ca^{2+} ultimately has to be removed from the cell to maintain its low intracellular level. Export of Ca^{2+} is accomplished by two mechanisms, an energy-consuming, ATP-driven Ca^{2+} pump and an electrogenic Ca^{2+}/Na^{+} exchange system making use of the energy provided by the sodium electrochemical gradient (ATP is consumed later by the ATP-driven sodium pump extruding Na^{+} against its gradient). The high affinity/low capacity Ca^{2+} pump, physiologically engaged in regulating the resting level of Ca^{2+}, is supported by the low affinity/high capacity Ca^{2+}/Na^{+} exchanger in times of increased neuronal activity in order to rapidly eliminate Ca^{2+}. From an energetic point of view, taking the detour via Na^{+} exchange seems to be a disadvantage for the cell. However, it appears as if the cell rather prefers dealing with Na^{+} than handling high amounts of the potentially harmful Ca^{2+}. This benefit is dearly bought, taking into account that, under pathological conditions, the Ca^{2+}/N^{+} exchanger can operate the reverse way, potentiating the calamitous sequelae of Ca^{2+} overload. Taken together, the above mentioned processes result in an almost constant cycling of Ca^{2+} across biological membranes at the substantial expense of energy.

CALCIUM AND ENERGY HOMEOSTASIS

Physiological conditions

It is generally appreciated that all the processes associated with increases in the cytosolic concentration of Ca^{2+} are energy-requiring and that therefore such events have also to be accompanied by compensatory stimulation of oxidative metabolism to produce ATP at enhanced rates (Denton and McCormack, 1985). Historically, the activation of energy metabolism was thought to be subject to substrate–product feedback control: Stimulation of cytosolic ATP-consuming processes effect a decline of the ATP/ADP ratio. According to evidence obtained with isolated mitochondria, the cellular power station, a fall in ATP/ADP resulted in an increased flow of electrons along the respiratory chain and increased O_2 consumption. Moreover, with regard to Ca^{2+} homeostasis, mitochondria were regarded as sinks for Ca^{2+}, buffering excessive Ca^{2+} to protect the cytosol against damage due to high Ca^{2+}. In vertebrate cells, this concept was questioned in its exclusive validity by findings demonstrating an increased cytosolic Ca^{2+} concentration coincident with an increased rate of respiration without decreases or even with increases of ATP/ADP ratios (Moreno-Sanchez, 1985). During the last 10–15 years a wealth of convincing data has led to an alternative concept, initially emerging from studies in liver and heart cells and recently extended to neurons (reviewed by Duchen *et al.*, 1993; McCormack and Denton, 1994; Gunter *et al.*, 1994).

The concept has been termed 'stimulus-response–metabolism coupling', appreciating the universal nature of Ca^{2+} as a signal adapting the supply of high-energy phosphates to the stimulus-evoked energy demand (McCormick and Denton,

1986). Regarding the nervous system, it has been shown that neuronal activity and neurotransmission increase oxygen and glucose consumption (Larrabee, 1967; Kennedy *et al*., 1992) and Ca^{2+}-dependent mitochondrial energy production (Erecinska *et al*., 1991). A rise of intracellular Ca^{2+} is associated with mitochondrial Ca^{2+} uptake (Ricken *et al*., 1998) and subsequent stimulation of pyruvate dehydrogenase (PDH) (Hansford *et al*., 1989) and the rate-limiting enzymes of the tricarboxylic acid cycle, which are all up-regulated by Ca^{2+} (Duchen *et al*., 1993; Hansford and Zorov, 1998). Additional evidence indicates that Ca^{2+} affects mitochondrial function at several sites between NADH oxidation and oxidative phosphorylation at the ATPase (Gunter *et al*., 1994; Mildaziene *et al*., 1996; Hansford and Zorov, 1998). Thus, changes in neuronal intracellular Ca^{2+} concentration within a physiological range, e.g. due to synaptic activity, promote significant and long-lasting changes of mitochondrial Ca^{2+} oscillations, potential and energy production (Duchen, 1992; Bindokas *et al*., 1998; Marhl *et al*., 1998; Simpson and Russell, 1998). Recently, the complete cascade of hormone-induced cytosolic Ca^{2+} increase, mitochondrial Ca^{2+} influx, PDH and respiratory chain activation and increase of mitochondrial membrane potential and proton motive force has been demonstrated (Robb-Gaspers *et al*., 1998).

The mitochondrial Ca^{2+} transport mechanisms merit further examination, since their features affect mitochondrial behaviour under physiological and pathological conditions. Ca^{2+} is transported into the mitochondria by a very fast electrophoretic uniporter which, in an energetic downhill process, is utilizing the negative transmembrane potential set up across the inner membrane by the protonmotive gradient of the respiratory chain. Recently described, another mechanism appears to be adapted for sequestering physiological Ca^{2+} transients or pulses (Gunter *et al*., 1998). At the beginning of a Ca^{2+} pulse its conductivity is much higher than the uniporter uptake, but decreases very rapidly following the increase of cytosolic Ca^{2+}. The major mitochondrial Ca^{2+} export pathway is by electroneutral $Ca^{2+}/2Na^{+}$ exchange. Again, the driving force for this exchange is taken from the protonmotive gradient by subsequent Na^{+}/H^{+} exchange. Another efflux mechanism which is of inferior importance in the brain is Na^{+}-independent, perhaps catalyzing direct Ca^{2+}/nH^{+} exchange. By means of these transport processes Ca^{2+} is cycled effectively across the inner mitochondrial membrane at the expense of energy, totalling less than 1 per cent of the respiratory capacity. Importantly, the uptake pathway has an approx. 10-fold higher maximal capacity compared with the egress pathways (Crompton, 1990). Under normal cellular conditions it is thought that uptake rates will always remain below the maximal capacity of the extrusion systems so that the values of mitochondrial and cytosolic Ca^{2+} will broadly reflect one another. However, if the cytosolic Ca^{2+} concentration rises above the normal physiological range (>1–2 μM), uptake will exceed egress and mitochondria will accumulate Ca^{2+} and can behave as buffers of cytosolic Ca^{2+} (Ricken *et al*., 1998). In neurons, at least in subpopulations, the set point at which buffer mechanisms come into play may be shifted to somewhat lower cytosolic Ca^{2+} values around $0{\cdot}5$ μM, values which can be reached physiologically after intense stimulation (Werth and Thayer, 1994). However, the ability of mitochondria to act as cellular Ca^{2+} sinks is limited.

Pathological conditions

Behaviour of mitochondria under pathological conditions is characterized by a phenomenon called permeability transition (PT) (recently reviewed by Gunter *et al*., 1994; Ichas and Mazat, 1998; in neurons demonstrated by Dubinsky and Levi, 1998). The transition is believed to be mediated by a large (estimated diameter 2–3 nm) proteinaceous pore in the matrix-delimiting envelope, whose molecular identity has not yet been fully established. The pore appears to operate at the interface of two distinct physiological pathways, the mitochondrial Ca^{2+} signalling network and the effector phase of cell death (Jouaville *et al*., 1998; Lemasters *et al*., 1998; Miller, 1998; for a discussion of apoptosis see also part II of this series). In a pH-operated, low-conductance state diffusion of small ions like Ca^{2+} is allowed. The high-conductance state is characterized by an increase of the permeability of the mitochondrial inner membrane to small ions and molecules, eventually followed by the loss of matrix proteins, leading to complete collapse of the membrane potential, to colloid-osmotic swelling of the mitochondrial matrix and the release of proapoptotic factors. Switching from low- to high-conductance state is an irreversible process, strictly dependent on the saturation of the Ca^{2+}-binding sites at the matrix-side in the presence of inducing

agents like oxidizing agents including radical-generating species, depolarization of the mitochondrial membrane, and inorganic phosphate (Kristal and Dubinsky, 1997). Both the increased permeability and drop of membrane potential is thought to be mediated by oxidative stress-induced protein aggregation following protein thiol cross-linking (Castilho *et al*., 1996). In the absence of an inducer, Ca^{2+} alone at values >100 μM can trigger the PT and it has been suggested that *in vivo* the PT may work as a fast, inducible Ca^{2+} release channel (Bernardi and Petronilli, 1996). Inhibition of opening is accomplished by physiological transmembrane potentials, divalent cations such as Mg^{2+}, antioxidants, and ADP. The most potent known inhibitor of PT is the cyclic immunosuppressive peptide cyclosporine A which competitively blocks the binding of Ca^{2+} to the pore.

These features of PT set the framework for mitochondrial disruption in pathological conditions. In brain, energy deprivation as in ischemia, hypoxia and hypoglycemia in a sequence of events causes significant rises in intracellular Ca^{2+} and anorganic phosphate from adenine nucleotide breakdown, a decrease of mitochondrial membrane potential and oxidative stress, known inducers of the Ca^{2+}-triggered PT which eventually will cause mitochondrial damage. Ca^{2+} not only launches the cascade but also controls individual steps in the generation and effector functions of reactive oxygen species (ROS) (reviewed by Vercesi *et al*., 1997). ROS are a mitochondrial product generated during reduction of molecular oxygen and leak from the respiratory chain even under physiological conditions (up to 2 per cent of the oxygen consumed) (Richter *et al*., 1995; Kowaltowski and Vercesi, 1998). At subtoxic levels, ROS including nitric oxide (NO), which are potent vascular relaxants, may fulfil physiological functions for maintenance of cellular Ca^{2+} homeostasis (Richter *et al*., 1995) and by adapting cerebral blood flow and tissue perfusion to the energetic needs (Brian *et al*., 1996).

Exposure of neuronal mitochondria to elevated Ca^{2+} under normoxic conditions results in the generation of ROS (reviewed by Kowaltowski and Vercesi, 1998). Evidence suggests that Ca^{2+} itself reverses the flow of electrons or stimulates electron leakage from the respiratory chain (Zhang *et al*., 1990; Paraidathathu *et al*., 1992; Castilho *et al*., 1995), presumably at the coenzyme Q level (Kowaltowski *et al*., 1995), increasing the mitochondrial production of ROS. Ca^{2+} binding to the inner mitochondrial membrane and ensuing alterations of its properties are causal (Kowaltowski *et al*., 1998). In a feed-forward cycle, radical exposure sustains subsequent radical production leading to further impairment of the electron transport complex activity (Dykens, 1994). NO, by competitively binding to the oxygen binding site of cytochrome oxidase, additionally inhibits mitochondrial respiration (Brown, 1997). Ca^{2+} and ROS regulate and eventually can elevate each other in an amplifying feedback/-forward cycle (Brorson and Zhang, 1997; Joseph *et al*., 1997, Richter, 1997): For instance, oxidative stress impairs the cells' ability to extrude excess Ca^{2+} after depolarization (Joseph *et al*., 1997), while removal of extracellular Ca^{2+} mitigates delayed ROS neurotoxicity, underlining the control of ROS effector functions by Ca^{2+} (Brorson and Zhang, 1997). Even PT could be achieved by Ca^{2+} under anaerobic conditions, indicating that mitochondria-generated ROS may not be a necessary prerequisite of PT (Kuzminova *et al*., 1998), while anaerobiosis prevented the mitochondrial PT in another study (Kowalowski *et al*., 1996). Finally, inhibition of the mitochondrial Ca^{2+}-cycling (by cyclosporine A and other PT blockers) effectively could protect mitochondria from the deleterious effects of free radicals, suggesting that Ca^{2+}-dependent PT and not direct ROS-related impairment of the mitochondrial inner membrane enzymes mediates the mitochondrial killing (Takeyama *et al*., 1993; Nicholls and Budd, 1998; Tanaka *et al*., 1998). Thus, ROS are not neurotoxic in the absence of mitochondrial Ca^{2+} accumulation (Nicholls and Budd, 1998). This causal relationship is also suggested by the temporal relationship in the induction of PT: intramitochondrial Ca^{2+} parallels the fall in mitochondrial membrane potential and precedes the accumulation of ROS (Wadia *et al*., 1998). These pathophysiological phenomena lead to a U-shaped Ca^{2+} concentration/oxidative phosphorylation relationship. In rat liver cells, optimal ATP synthesis takes place at cytosolic Ca^{2+} concentrations of 0·5–1·0 μM with lower effectivity at lower and higher Ca^{2+} levels (Moreno-Sanchez, 1985). Not only can an increase of cellular Ca^{2+} concentration lead to mitochondrial damage and energetic compromise, the converse way is also feasible in that inhibition of bioenergetics and collapse of the mitochondrial potential increased intracellular Ca^{2+} (Ray *et al*., 1994; Khodorov *et al*., 1996) and Ca^{2+} influx through voltage-gated channels (Nowicky and Duchen, 1998). Thus, in

pathogenetically ill-defined situations a chicken–egg conundrum may prevail.

THE CALCIUM–ENERGY–REDOX TRIANGLE IS REGULATED BY HORMONES

The preceding chapters emphasized the fundamental importance of the calcium–energy–redox triangle for the cellular trophism. Unicellular organisms 'learned' to maintain their internal homeostasis under a variety of external signals conveyed by a multitude of ambient conditions and nutritional supplies. With the evolutionary rise of multicellular organisms, the external milieu was increasingly replaced by a better controllable internal milieu. Differentiated cells with divergent cellular functions, and hence different homeostatic requirements, evolved. In this internal milieu, an array of mediators, whose signals are transduced by a multitude of receptors, provides a homeostatic support according to the spatial, temporal and functional needs of specialized cells. The nervous system as both most energy-consuming and -dependent organ (reviewed by Magistretti *et al*., 1995) elaborated a highly sophisticated network of interrelated systems to ensure the energy-dense milieu which is indispensable for the functioning of this excitable tissue.

THE ROLE OF NEUROPEPTIDES AND -HORMONES IN NEURONAL TROPHISM

In the last 15 years, knowledge about both neuropeptides and neurohormones has been greatly expanded. It has emerged that these powerful substances, by their autocrine, paracrine and endocrine actions, are involved in the regulation and modulation of neuronal development, trophism and repair (reviewed by, for example, Annals of the New York Academy of Sciences vols. 611, 692, 697, 719, 739, 746, 774, 780, 839). Often coexisting with classical neurotransmitters, they participate in signalling at synaptic and nonsynaptic sites and particularly play an important role in intercellular communication as volume transmission signals (Fuxe *et al*., 1994). Preferentially conferring a slow, long-lasting, syndromic message (Fuxe *et al*., 1994), they modulate neuronal energy homeostasis and excitability, regulate neurotransmitter balances and drive circadian rhythms. While the fast and short acting neurotransmitters have key roles in acute syndromes such as stroke, persistently acting neuropeptides/-hormones may be prime candidate effectors in the pathophysiology of chronic syndromes like ageing or AD. In the context of this work, from the multitude of neuropeptides/hormones only those are covered with known neurotrophic or -aggressive actions and known secretion/receptor changes during ageing. As we are at the beginning of a rapid scientific development, it can be expected that the list of these agents will be extended. In a first step, these agents and their neuromodulatory roles with regard to the homeostatic triangle are discussed.

Neuropeptide Y

Neuropeptide Y (NPY), a 36 amino acid peptide transmitter is widely distributed throughout the CNS (Brene *et al*., 1989; Aoki and Pickel, 1990). NPY is known to be involved in the central regulation of appetite, sexual behaviour, energy homeostasis, reproductive function and the hypothalamic-pituitary-adrenal (HPA)-axis (Kalra and Kalra, 1996). NPY has a physiological role in information handling (Fuxe *et al*., 1990) and as a modulator of memory processing enhances retention and recall (Flood *et al*., 1989; Morley and Flood, 1990). NPY has been implicated in the modulation of neuronal excitability (Colmers and Bleakman, 1994). NPY inhibits and controls hippocampal seizures (Woldbye *et al*., 1996; Baraban *et al*., 1997) and epileptiform neuronal activity (Smialowska *et al*., 1996a; Klapstein and Colmers, 1997), and mice lacking NPY exhibit an increased susceptibility to seizures (Erickson *et al*., 1996; Baraban *et al*., 1997). NPY controls neuronal excitation by inhibition of impulse-dependent synaptic excitation (McQuiston and Colmers, 1996), by presynaptic inhibition of excitatory transmission (Colmers, 1990), inhibition of glutamatergic transmission (Van den Pol *et al*., 1996) and glutamate release (Greber *et al*., 1994; Bleakman *et al*., 1997), activation of inwardly rectifying K^+ currents (Sun *et al*., 1998) and depression of L-type, N-type and P/Q-type Ca^{2+} currents in a variety of neurons (Hirning *et al*., 1990; McCullough *et al*., 1998; Sun *et al*., 1998). An NPY stimulated Na^+-dependent Ca^{2+} efflux may further contribute to the optimization of cellular Ca^{2+} homeostasis (Horike *et al*., 1997). Intraventricular NPY improves the economy of energy homeostasis, it increases the respiratory quotient, reduces energy expenditure, and stimulates glucose turnover (Marks and Waite, 1997). Behaviourally, NPY counteracted

amphetamine-induced hyperactivity (Smialowska *et al*., 1996b), and was anxiolytic and protective against stress (Wahlestedt and Heilig, 1995).

Dehydroepiandrosterone (DHEA) and DHEA sulfate

Pregnenolone, derived from cholesterol, is the precursor for all three groups of adrenal steroids. In human, DHEA and its sulfate (DHEAS) are the most abundant adrenal steroid hormones. It has pleiotropic biological functions (see Kalimi and Regelson, 1990). DHEA is metabolized into testosterone or oestrogen by the gonads. DHEA is also a neuroactive neurosteroid which is synthesized and metabolized in the brain independent of peripheral levels (Corpechot *et al*., 1981; Majewska, 1995; Robel and Baulieu, 1995). In the brain, DHEA-synthesizing enzymes are developmentally and region-specifically regulated and DHEA/DHEAS differentially promote the growth of neurites in a polarity-specific fashion (Compagnone and Mellon, 1998). DHEA has multiple effects on cellular energy metabolism. It stimulated glucose uptake and expression of glucose transporter in human fibroblasts (Nakashima *et al*., 1995), improved efficiency of oxygen utilization at the tissue level (Schauer *et al*., 1990) and elevated mitochondrial respiration (Mohan and Cleary, 1991; McIntosh *et al*., 1993). DHEA has antioxidant properties (Tamagno *et al*., 1998). It induces glutathione (White *et al*., 1998), prevents the reduction of tissue vitamin E and A under stressful conditions (Araghi-Niknam *et al*., 1998), inhibits the ischemia-induced generation of reactive oxygen species (Delbarre *et al*., 1995), prevents the oxidative damage induced by acute hyperglycemia (Aragno *et al*., 1997) and protects serum lipoproteins from peroxidation *in vitro*, in elderly humans and infected mice (Araghi-Niknam *et al*., 1998; Khalil *et al*., 1998). The cytotoxic effects of a mitochondrial inhibitor or hypoxia could be blocked completely by DHEAS (Waters *et al*., 1997). Hippocampal toxicity of NMDA or glucocorticoids was blocked by DHEA/DHEAS *in vivo* and *in vitro* (Kimonides *et al*., 1998; Mao and Barger, 1998). The neuroprotective activity of DHEAS may be dependent on the activation of $NF_{\kappa}B$-like factor (Mao and Barger, 1998). DHEAS can rapidly depress neuronal voltage-gated Ca^{2+} currents (ffrench-Mullen and Spence, 1991), it increased neuronal excitability by modulating GABA inhibition (Meyer and Gruol, 1994; Steffensen, 1995) and enhanced hippocampal LTP and primed burst potentiation (Diamond *et al*., 1995; Yoo *et al*., 1996), putative electrophysiological correlates of learning (Bliss and Collingridge, 1993). DHEAS inhibits intracellular GABA- and NMDA-mediated Ca^{2+} increases in primary cultured neurons (Inagaki *et al*., 1997). Both DHEA and DHEAS improved memory in young and ageing mice (Roberts *et al*., 1987; Flood and Roberts, 1988) and enhanced neuronal and glial survival and differentiation in culture (Bologa *et al*., 1987; Roberts *et al*., 1987). Possibly, the cognition enhancing effect can be attributed to DHEAS, since it enhances hippocampal ACh release (Rhodes *et al*., 1996) and an almost three-fold increase of hippocampal acetylcholine release and inhibition of scopolamine-induced amnesia could be achieved in rats by administration of a sulfatase inhibitor that blocks the conversion of DHEAS to DHEA (Rhodes *et al*., 1997).

Gonadal steroids

Gonadal steroids exert various neurotrophic influences both by genomic and non-genomic actions (reviewed by Jones, 1993). Sex hormone regulation of synaptic connections and neurite outgrowth has been demonstrated. Oestrogen (E) and β-oestradiol (E2), a metabolite of E and testosterone (T), promote neurite outgrowth, dendritic differentiation and number of synapses *in vitro* and, in various regions of the brain, *in vivo* (reviewed by Frankfurt, 1994). Particularly, plasticity of septal cholinergic neurons is enhanced (Mudd *et al*., 1998). E secretion across the oestrous/menstrual cycle effects phasic fluctuations of synaptic densities and shift of optimal computational functions (Desmond and Levy, 1997). The sprouting promoting effect of E2 is dependent on apoE (Stone *et al*., 1998) and mediated by NMDA receptors (Brinton *et al*., 1997). Levels of choline acetyltransferase (ChAT) activity, neurotrophins and their receptors fluctuate across the oestrous cycle and increase in response to acute E administration (Gibbs, 1994; Gibbs and Aggarwal, 1998). Gonadectomy reduced and E/E2 replacement increased ChAT activity and nerve growth factor receptor mRNA in basal forebrain and frontal cortex of female and male rats, epitomizing the profound effects of E/E2 on the cholinergic/neurotrophic system (reviewed by Gibbs, 1994; Gibbs and Aggarwal, 1998). Both E and E2 protect and rescue neurons *in vitro* against death from a variety of stressors (Behl *et al*., 1995;

Green *et al*., 1997; Weaver *et al*., 1997; Singer *et al*., 1998). Moreover, E2 protected female rats from ischemia-induced neurodegeneration *in vivo* and reduced mortality in an animal model of stroke (Simpkins *et al*., 1997; Dubal *et al*., 1998). Cerebral energy metabolism, compromised following intracerebroventricular streptozotocin, was almost completely normalized by E2 (Lannert *et al*., 1998). The phenolic A ring is required for the neuroprotective action of E and E2 (Green *et al*., 1997), a finding which stresses the importance of the aromatization of T in the male brain.

These neurotrophic/-protective effects may depend on Ca^{2+}-regulatory, antioxidant and metabolism-enhancing effects. E/E2 exhibit Ca^{2+} antagonist properties (Collins *et al*., 1996; Mermelstein *et al*., 1996), modulate the activity of the Mg^{2+}-dependent Ca^{2+}-ATPase (Zylinska and Legutko, 1998) and inhibit NMDA receptors (Weaver *et al*., 1997). A suppression of membrane lipid peroxidation (Keller *et al*., 1997) and neuroprotective synergism between E2 and glutathione (Gridley *et al*., 1998) suggest an antioxidant potential of E/E2. Structurally, the antioxidant activity of oestrogens seems to be related to the hydroxyl group at the C3 position of the A ring and independent of an activation of E receptors (Behl *et al*., 1997a). The cellular energy metabolism is augmented by stabilization of mitochondrial transmembrane potential and function (Mattson *et al*., 1997), induction of cytochrome c oxidase (Bettini and Maggi, 1992) and increase of glucose transport, uptake and utilization through induction of key glycolytic enzymes (Nehlig *et al*., 1985; Kostanyan and Nazaryan, 1992; Bishop and Simpkins, 1994). The anti-apoptotic activity exerted by E may be mediated by expression of Bcl-related proteins (Garcia-Segura *et al*., 1998; Singer *et al*., 1998). In addition, the neurotrophic activity of E may, at least in part, be mediated by the increased expression of IFG-1 (Shingo *et al*., 1997). E/E2 improve specific cognitive functions in both females and males, at least in part, by interacting with the cholinergic system (reviewed by Sherwin, 1994; Packard, 1998).

Melatonin

Melatonin (M), a derivative of serotonin is produced and secreted by the pineal gland in a circadian rhythm with highest blood levels of the hormone being present during the night. The hormone cycle drives other diurnal rhythms as well as seasonal cycles of reproduction. M has been recognized as a specific free radical scavenger and, being highly lipophilic, is highly potent to protect intracellular molecules from oxidative damage (reviewed by Reiter *et al*., 1997). Moreover, M increases the gene expression for various antioxidant enzymes in rat brain (Kotler *et al*., 1998) and maintains glutathione homeostasis under excitotoxic challenge (Floreani *et al*., 1997). M effects are also mediated by specific G-protein-coupled high-affinity receptors (Vanecek, 1998). Via these receptors, M regulates several second messengers: cAMP, cGMP, diacylglycerol, inositol trisphosphate, arachidonic acid, and Ca^{2+} (Vanecek, 1998). For instance, M is able to depress K^{+}-stimulated Ca^{2+}-uptake into rat synaptosomes (Vacas *et al*., 1984). Additionally, M is a high-affinity Ca^{2+}/calmodulin antagonist, thereby blocking Ca^{2+} actions and modulating rhythmically many cell functions (Benitez-King and Antontay, 1993; Huerto-Delgadillo *et al*., 1994).

In hippocampal neurons, M depresses synaptic transmission, hyperpolarizes the membrane potential, increases the duration of the action potential, shifts the threshold for the triggering of action potentials, prolongs inhibitory potentials and abolishes repetitive spiking elicited by GABA antagonists (Zeise and Semm, 1985; Gonzales and Armstrong, 1995). These features, together with a putative GABA-enhancing potential (Stankov *et al*., 1992), allow M to attenuate CNS excitability and to exert a neuroprotective role (Acuna-Castroviejo *et al*., 1995). Thus, M has antiepileptic properties in various animal models and possibly in humans (Fauteck *et al*., 1995; Molina-Carballo *et al*., 1997; Lapin *et al*., 1998), while antimelatonin antibodies induced epileptogenic activity (Fariello *et al*., 1977). Moreover, M protects neurons against neurotoxic actions of excitotoxins like kainate, NMDA (Giusti *et al*., 1996; Cazevielle *et al*., 1997; Skaper *et al*., 1998a) and against traumatic brain injury, hypoxia/reoxygenation and ischemia (Cazevieille *et al*., 1997; Cho *et al*., 1997; Mesenge *et al*., 1998), the latter by inhibiting NO and hydroxyl radical production (Guerrero *et al*., 1997; Li *et al*., 1997). Likewise, M reduced *in vivo* and *in vitro* apoptotic cell death mediated by singlet oxygen (Maney *et al*., 1995) and DNA strand breaks induced by electromagnetic fields (Lai and Singh, 1997). In contrast, M-deficient rats exhibited increased brain vulnerability in stroke and excitotoxicity (Manev *et al*., 1996).

Neurotrophins

The neurotrophins are structurally related polypeptides that make up one family of neurotrophic factors. Nerve growth factor (NGF) is the best-characterized member of this family (reviewed by Guroff, 1993; Levi-Montalcini *et al*., 1996), which includes brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4/5 (Thoenen, 1991; Bradshaw *et al*., 1993). These proteins bind to and stimulate Trk-type tryosine kinase receptors (Barbacid, 1995; Bothwell, 1995) and a low-affinity receptor called p75 (Chao, 1994) which reciprocally modulate their affinity states (Ross *et al*., 1998). Other neurotrophic factors include IGFs (see below), fibroblast growth factors (FGFs), epidermal growth factors (EGFs), ciliary neurotrophic factor (CNTF), transforming growth factor-β (TGFβ) and others (see Hefti, 1997). An adequate appreciation of all these factors goes beyond the scope of this paper. Hence, focus will be on NGF and related agents.

Neurotrophins represent a family of growth, differentiation and survival factors with profound effects in the central and peripheral nervous system (Johnson and Yip, 1985; Barde, 1994). The requirements of cell populations for individual growth factors differ dependent on developmental status, transmitter phenotype, function, brain region and stressor type (Edgar *et al*., 1981; Shelton and Reichardt, 1986; Maisonpierre *et al*., 1990; Friedman *et al*., 1993; Nonner *et al*., 1996; Skaper *et al*., 1998b). For instance, NGF is intimately associated with the cholinergic system (Korsching *et al*., 1985), while initial evidence indicates a neuroprotective activity of BDNF for serotonergic neurons (Mamounas *et al*., 1995), and of NT-3 and NT-4/5 for noradrenergic locus coeruleus neurons (Friedman *et al*., 1993; Arenas and Persson, 1994).

In the mature CNS the production of neurotrophins is regulated by hormones, neuronal activity and integrity and a variety of stressors (Gall and Isackson, 1989; Castren *et al*., 1993; Lindholm *et al*., 1994a; Lindvall *et al*., 1994). Mechanistically, these events depend on both glutamatergic and cholinergic activity and Ca^{2+} influx or release (Thoenen *et al*., 1991; Lindefors *et al*., 1992; Kokaia *et al*., 1993; Ghosh *et al*., 1994; Knipper *et al*., 1994). By controlling neurotransmission, connectivity and neurite outgrowth, neurotrophins are pivotal regulators of neuronal plasticity (Crutcher, 1986; Kang and Schuman, 1995). Trophic effects of neurotrophins are dependent on target-derived retrograde transport (Hendry *et al*., 1974; Korsching and Thoenen, 1983; Kromer, 1987), anterograde supply from the cell body to the nerve terminal followed by axodendritic transfer (von Bartheld *et al*., 1996; Altar and DiStefano, 1998), as well as on autocrine/paracrine actions (Ghosh *et al*., 1994; Lindholm *et al*., 1996; Johnson *et al*., 1997). Upregulated by a variety of stressors, neurotrophins protect and rescue the neonatal and mature brain against these stressors (reviewed by Mattson *et al*., 1993), such as oxidative stress, excitotoxicity (Cheng *et al*., 1994; Skaper *et al*., 1998b), hypoglycemia (Cheng *et al*., 1994; Kokaia *et al*., 1994; Nonner *et al*., 1996), hypoxic-ischemic injury (Mattson and Cheng, 1993; Holtzman *et al*., 1996), traumatic brain injury (Sinson *et al*., 1997), mitochondrial inhibition (Frim *et al*., 1993), deafferentation (Johnson *et al*., 1997), and enhance neurite regeneration (Horie *et al*., 1991). Remarkably, neurotrophins stimulate the neuronal expression of NPY, somatostatin and substance P, thus reinforcing their neuroprotective activity (Carnahan and Nawa, 1995).

The neurotrophic and neuroprotective actions of neurotrophins are mediated by their regulation of neuronal energy homeostasis through modulation of glucose utilization, energy production, Ca^{2+} and antioxidant homeostasis (Jackson *et al*., 1994). Neurotrophins enhance glucose uptake and utilization, increase mRNA and biochemical activity of enzymes of the glycolytic pathway, and increase cellular content of energy-rich phosphates (Liuzzi *et al*., 1968; Skaper and Varon, 1979; Morelli *et al*., 1986). The neurotrophins upregulate various antioxidant enzyme systems and thus increase resistance to oxidative stress (reviewed by Sampath and Perez-Polo, 1997). The neurotrophins and Ca^{2+} establish another feedback cycle in which mutual interdependencies are determined by set points (Koike and Tanaka, 1991). Ca^{2+} influx regulates the expression of neurotrophins (Ghosh *et al*., 1994; Shieh *et al*., 1998; Tao *et al*., 1998), while, on the other hand, the neurotrophins help to maintain Ca^{2+} homeostasis (Jiang and Guroff, 1997; Dispersyn *et al*., 1998). This capacity is possibly mediated by the expression of Ca^{2+}-binding proteins. NGF elevated calretinin mRNA levels, while BDNF increased calbindin mRNA and decreased calretinin mRNA levels (Fiumelli *et al*., 1997; Isaacs *et al*., 1997). NGF-mediated upregulation of the Ca^{2+}-ATPase expression is another mechanism by which cytosolic Ca^{2+} levels can be stabilized (Garcia *et al*., 1997). Finally, bcl-2, an

anti-apoptotic agent, is upregulated by NGF, effecting the rescue from apoptosis (Katoh *et al*., 1997).

Insulin and insulin-like growth factors

Insulin and insulin-like growth factors (IGF) 1 and 2 are members of a structurally related family of proteins which are essential to normal metabolism and growth. Circulating IGFs are regulated by growth hormone. In the brain they are synthesized locally as well as being taken up from the peripheral circulation (Adamo *et al*., 1989). Insulin and IGF actions are mediated by binding to a family of receptors (IGFR) which are expressed throughout the brain, particularly in large projecting neurons with an elaborate dendritic arbor. Hence, the pattern of IGFR distribution correlates closely with metabolic activity (reviewed by Bondy and Lee, 1993).

Insulin and IGFs play an important role in the normal development, differentiation, maintenance of neuronal integrity and survival (reviewed by Ishii, 1993; D'Ercole *et al*., 1996; Feldman *et al*., 1997). Transgenic mice, overexpressing IGF-1, exhibited an increased brain growth and myelination (Carson *et al*., 1993). IGF-1 gene disruption, on the other hand, results in reduced brain size, CNS hypomyelination and a loss of distinct hippocampal and striatal neuronal populations (Beck *et al*., 1995). A multitude of organs, such as liver, kidney, heart, and brain, have been shown to respond to a variety of stressors by expressing a coordinated pattern of IGFs, IGF binding proteins and IGF receptors (IGFR). In the brain, tissue injuries due to ischemia, contusion, cryogenic or cytotoxic lesions, autoimmune encephalomyelitis, deafferentation, axotomy, and penetrating wounds induced expression of IGFs by astrocytes and microglia and IGFR by neurons, suggesting an autocrine/paracrine action in neuronal rescue and repair (Gluckman *et al*., 1993; Bondy and Lee, 1993; Guthrie *et al*., 1995; Sandberg-Nordqvist *et al*., 1996; Walter *et al*., 1997). Treatment with insulin and IGF-1 protects and even rescues neurons against damage induced by ischemia (Gluckman *et al*., 1993; Zhu and Auer, 1994; Johnston *et al*., 1996), glucose deprivation and impairment of energy production (Mattson and Cheng, 1993), and oxidative stress (Sortino and Canonico, 1996). Moreover, IGF-1 improves nerve regeneration (Vergara *et al*., 1993) and promotes neurite growth (Ang *et al*., 1993).

Either insulin or IGF-1 inhibit neuronal apoptosis induced by serum deprivation (Ryu *et al*., 1997), osmotic stress (Mathews and Feldman, 1996), NO and NMDA (Tagami *et al*., 1997), K^+ withdrawal (Atlante *et al*., 1998) and inhibition of protein phosphatases (Fernandez-Sanchez *et al*., 1996). Mechanisms by which insulin and IGFs protect neurons may include effects on energy and Ca^{2+} homeostasis. The impairment of mitochondrial respiration is prevented (Atlante *et al*., 1998). Insulin and IGF-1 upregulate the brain glucose transporter through independent pathways at the transcriptional and posttranscriptional level (Werner *et al*., 1989). Glycolytic metabolism is highly compartmentalized in the brain and predominantly takes place in astrocytes which supply neurons with lactate (Magistretti *et al*., 1995). Insulin and IGF-1 enhance astrocytic glycolysis, while neurons are stimulated to release factors which upregulate astrocytic lactate production (Sonnewald *et al*., 1996). The enhancement of the neurotrophic activity of various growth factors by astrocytes (Ang *et al*., 1993) may depend on this metabolic symbiosis. Additionally, IGF-1 blocked intraneuronal free Ca^{2+} elevations (Cheng and Mattson, 1992), modulated Ca^{2+} currents (Kleppisch *et al*., 1992), and increased expression of calretinin and calbindin (Nieto-Bona *et al*., 1995; Yamaguchi *et al*., 1995). Finally, IGFs appear to reduce brain blood flow resistance (Gillespie *et al*., 1997).

Somatostatin

Somatostatin (SS) is a tetradecapeptide which is widely distributed in the CNS, particularly in the hypothalamus, neocortex and all limbic structures (reviewed by Rubinow *et al*., 1995). During neuronal development, SS acts as a trophic peptide (Schwartz *et al*., 1996), effecting maturation of dendritic trees and promoting dendritic complexity (Kungel *et al*., 1997). SS protects cultured cortical and striatal cells against NMDA-induced toxicity (Forloni *et al*., 1997; Patel *et al*., 1997). Similar to NPY, a wealth of findings (reviewed by Rubinow *et al*., 1995) argues for an important role of SS in seizure susceptibility and counterregulatory activity.

Several mechanisms may jointly determine the neurotrophic/-protective actions of SS. SS depresses neuronal excitability (Jacquin *et al*., 1988; Lu *et al*., 1995), decreases intracellular Ca^{2+} by dose-dependently inhibiting Ca^{2+} channel activity (Kleuss *et al*., 1991; Ishibashi and Akaike, 1995;

Traina *et al*., 1996), and reduces neuronal firing by hyperpolarization through activation of a voltage-dependent outward K^+ conductance (Mihara *et al*., 1987; Jacquin *et al*., 1988). The inhibitory actions include hyperpolarization of the postsynaptic membrane at rest and depression of AMPA and NMDA receptor-mediated excitatory currents, particularly during hyperexcited states (Tallent and Siggins, 1997). Moreover, SS enhances cortical and hippocampal glucose uptake (Shibata *et al*., 1993).

Thyroid hormones

Thyroid hormones (TH) thyroxine (T4) and triiodothyronine (T3) have a significant influence on the development and maturation of the CNS (Pasquini and Adamo, 1994). The special significance for the brain of a sufficient supply of TH is illustrated by the facts that (i) phylogenetically, the expression of the transthyretin (TT) gene, coding for the T4 transport protein, evolved in the brain 200 million years earlier than in the liver, (ii) the T4 binding structure has been conserved in evolution since 350 million years ago, (iii) genetic deficiencies are absent, (iv) TT, secreted by the choroid plexus, is the most abundant cerebrospinal fluid protein, accounting for 25 per cent of the ventricular proteins (reviewed by Schreiber *et al*., 1995). TH exert a variety of neurotrophic actions and control the temporal regulation of proliferation, differentiation and cell survival either directly or via the induction of neuronal growth factors (reviewed by Muller and Clos, 1997). Nuclear T3 receptors mediating the genomic actions of TH are expressed throughout the developing and adult brain in neurons, glial and ependymal cells in an area-specific distribution (Ruel *et al*., 1985; Puymirat *et al*., 1991). TH play a role in the developmental regulation of neurotrophins and neurotrophin-receptor levels (Luesse *et al*., 1998). They synergize with NGF in the regulation of a number of neuronal structures, particularly cholinergic neurones, in a region- and developmental stage-specific manner and increase neurite outgrowth and branching (Kalaria and Prince, 1985; Hashimoto *et al*., 1994; Luesse *et al*., 1998). The effects on neuronal and glial differentiation, polarity and branching are mediated by modulation of microtubule assembly and modification of developmental patterns of expression of microtubule proteins like actin, tubulin and tau (Aizenman and de Vellis, 1987; Aniello *et al*., 1991; Poddar *et al*., 1996).

Moreover, TH also have a role in adult brain plasticity and metabolism (reviewed by Calza *et al*., 1997a). TH increase the mRNA of NGF and NT-3 in adult rat hippocampus and ChAT activity in the cortex (Giordano *et al*., 1992) and also regulate NGF content and low affinity receptor expression in the basal forebrain (Calza *et al*., 1997b). TH affect mitochondrial functions in a U-shaped way, resulting in an optimal function at physiological levels and impaired functions with excess and deficiency (Popovici *et al*., 1980). Both short-term and long-term effects can be distinguished (Nelson, 1990). In development and maturity, mitochondrial respiration and oxidative phosphorylation is stimulated by TH in a variety of organs including the brain (Popovici *et al*., 1980; Nelson, 1990; Soboll, 1993; Katyare *et al*., 1994). Long-term influences of TH on mitochondrial activity include the expression of both nuclear and mitochondrial encoded respiratory genes (Nelson, 1990; Vega-Nunez *et al*., 1995; Pillar and Seitz, 1997), increase of the activity of TCA cycle enzymes (Diez-Guerra *et al*., 1981) and stimulation of mitochondrial oxygen consumption (Horst *et al*., 1989). The TH-induced alterations of phospholipid composition leading to increased membrane fluidity of mitochondria may contribute to these actions (Bangur *et al*., 1995). In the brain, the activity of glycolytic enzymes is increased (Sabell *et al*., 1985; Srivastava and Baquer, 1985) and the expression of the cerebral glucose transporter is modulated (Mooradian *et al*., 1997). TH affect the sarco(endo)plasmic reticulum and mitochondrial Ca^{2+} transport activity (Muller *et al*., 1991; Soboll, 1993) in part by regulating the expression of Ca^{2+}-ATPase (Rohrer and Dillmann, 1988; Cernohorsky *et al*., 1998), and decrease mitochondrial Ca^{2+} accumulation and retention (Grief, 1988). Furthermore, T3 improves neuronal transmission by enhancing synaptic Ca^{2+} uptake (Mason *et al*., 1990). TH have multiple effects on microtubule organization, regulating the splicing of juvenile and adult tau mRNA variants (Aniello *et al*., 1991). Finally, TH promote expression of the anti-apoptotic agent bcl-2 and prevent apoptosis (Muller *et al*., 1995).

The paramount importance of TH for even short-term adaptations of neuronal metabolic regulation was indicated by the dramatic rises of cerebral deiodinase activity (which converts T4 into the approx. five times more active T3) and T3 levels induced by a variety of acute stressful conditions (Friedman *et al*., 1997; Pinna *et al*., 1997). This can be interpreted as a compensatory neuroprotective

response to the detrimental effects of stressors as shown *in vitro* by T3 (Isaeff *et al*., 1993). Recent evidence suggests that T3 also subserves neurotransmitter functions in the adult brain, colocalizing with noradrenergic centres — locus coeruleus (LC) and lateral tegmental system — and being axonally transported to noradrenergic terminal fields (Dratman and Gordon, 1996). Since the noradrenergic LC is one of the central coordinators of the stress system (reviewed by Stratakis and Chrousos, 1995), the colocalization of T3 could imply a metabolic adaptation system to meet the increased metabolic demands exerted by central stress responses.

Thyrotropin releasing hormone (TRH), which is widely distributed in the brain (Kaji *et al*., 1993; Satoh *et al*., 1993), additionally has neuroprotective properties. TRH increases following seizure activity (Knoblach and Kubek, 1994), has anticonvulsant effects, and attenuates glutamate-induced neuronal Ca^{2+} increases (Koenig *et al*., 1996). TRH improved ageing-related deterioration of glucose utilization in various rat brain regions (Nakayama and Nagai, 1997). Recent evidence suggests a master function of the hypothalamic–pituitary–thyroid system in the regulation of genes critical for Ca^{2+} homeostasis. Thyroid transcription factor 1 (TTF-1) was identified as a key effector of thyroid-specific gene expression and was also found in the CNS. TTF-1 is modulated by a Ca^{2+}-sensing receptor (CSR) and as feed-forward leg may coordinately regulate a variety of genes involved in Ca^{2+} homeostasis, coding for CSR, calmodulin, and calcitonin, for example (Suzuki *et al*., 1998).

Substance P

Substance P (SP) is an undecapeptide whose receptors are distributed throughout the brain. High concentrations of receptor are present in the basal ganglia and amygdalo-hippocampal area, septum, nucleus basalis and locus coeruleus (Quirion *et al*., 1983; Mantyh *et al*., 1984). Raised SP levels may be one of the actions of NGF (Brewster *et al*., 1995). SP appears to stimulate monoaminergic neurons in the brain (Magnusson *et al*., 1976) and excites neurons in the nucleus basalis and locus coeruleus (Cheeseman *et al*., 1983; Nakajima *et al*., 1991). The excitatory action on nucleus basalis neurons may be instrumental in the memory-promoting and reinforcing properties of SP (reviewed by Huston and Hasenöhrl, 1995). SP may enhance oxidative phosphorylation (Prabhakar *et al*., 1989) and increases the Ca^{2+},Mg^{2+}-ATPase and Na^{+},K^{+}-ATPase activity from cortex and hippocampus (Wojtkowiak *et al*., 1990). These properties may underly its neurotrophic and neuroprotective actions (Whitty *et al*., 1993; Barker, 1996). SP can stimulate neurite outgrowth (Narumi and Maki, 1978) and promotes hippocampal neuronal survival (Whitty *et al*., 1993). Finally, SP can protect neurons against various neurotoxic agents (Jonsson and Hallman, 1982; Kowall *et al*., 1991; Sanberg *et al*., 1993).

Glucocorticosteroids

Glucocorticosteroids (GC) are secreted by the adrenal cortex as a physiological response to stimuli that threaten homeostasis. This stress response is a basic adaptive mechanism in mammals, involving the hierarchical hypothalamic–pituitary–adrenal (HPA) axis. Steroid receptors are found throughout the CNS, the low-affinity glucocorticoid receptors (GR) occurs in most neurons and glia, the high-affinity mineralocorticoid receptors (MR) predominantly in the limbic system. GC are important regulators of neuronal birth and differentiation in the midbrain–hippocampal axis, particularly of dentate gyrus granule cells, of serotonergic but also of cholinergic neurons (Azmitia and Liao, 1994; Gould, 1994; Berse and Blusztajn, 1997). GC are modulators of neuronal excitability (reviewed by Joels *et al*., 1994; Landfield and Eldridge, 1994). The relative occupation of MR and GR will determine the type of electrophysiological and genomic response. Particularly, the shift from predominant MR occupation to the situation where both MR and GR are activated is physiologically interesting. According to *in vitro* evidence, this transition is characterized by a considerable increase of Ca^{2+} currents due to modulation at genomic and non-genomic levels (Werkman *et al*., 1996; Nair *et al*., 1998). Thus, GC treatment enhances high voltage-activated calcium currents in cultured rat hippocampal neurons and slices (Porter *et al*., 1995; Coussens *et al*., 1997) and modulates Ca^{2+} channel mRNA expression (Nair *et al*., 1998), which, when sustained for an extended period, could result in elevated intracellular Ca^{2+} levels. GC affect the slow Ca^{2+}-dependent K^{+} conductance and hence the slow afterhyperpolarization (AHP), both of which are dependent upon the submembrane concentration of Ca^{2+} (reviewed by Disterhoft *et al*., 1996; Landfield, 1996); high-dose GC

increase the AHP and decrease hippocampal excitability. Presumably due to these electrophysiological effects, long-term potentiation (LTP) and primed-burst potentiation (PBP) are modulated biphasically by GC. Intermediate GC levels lead to a potentiation, while both lack and excess of GC have detrimental effects (reviewed by McEwen, 1994). GC disrupt neuronal and glial energetics by inhibition of glucose transport and utilization (Sapolsky, 1985; Virgin *et al*., 1991; Doyle *et al*., 1994). Mitochondrial respiratory rates are decreased and oxidative phosphorylation is uncoupled, resulting in decreased ATP synthesis (Jani *et al*., 1991; Martens *et al*., 1991). Thus, GC put predominantly hippocampal neurons under metabolic stress, rendering them vulnerable to a whole variety of noxious conditions like excitotoxicity, aglycemia, anoxia, ischemia, traumatic brain injury, oxidative stress, and seizures (reviewed by Sapolsky, 1994). Notably, both GC and stress synergize with excitotoxic damage to elicit neurofibrillary tangle-like antigenic changes in hippocampal neurons (Elliott *et al*., 1993; Stein-Behrens *et al*., 1993). In line with these notions, a GC receptor antagonist prevented intracellular peroxide accumulation and cell death induced by hydroxide and glutamate in rat hippocampal neurons and slices (Behl *et al*., 1997b). Similarly, an inhibitor of GC production reduced brain injury induced by ischemia and seizures (Smith-Swintosky *et al*., 1996). The Ca^{2+} influx appears to mediate the cellular damage, since a Ca^{2+} antagonist protected hippocampal neurons from GC induced damage (Dachir *et al*., 1997).

In addition, GC may elicit neuronal degeneration and inhibit neurite outgrowth by decreasing neurotrophic activity (Jap Tjoen San *et al*., 1992). Hippocampal neurotrophins, e.g. NGF, BDNF and NT-3 expression, may be depressed (Smith, 1996; Ueyama *et al*., 1997), while in other experimental settings NGF and NT-3 are increased by stress and GC (Mocchetti *et al*., 1996; Smith, 1996). The conflicting data may be reconciled by a model which suggests a U-shaped relationship between GC and neurotrophins (Lindholm *et al*., 1994b). Irrespective of their up- or downregulation, biological effects of neurotrophins may be attenuated, since their receptor expression is downregulated, receptor binding is decreased and downstream signal transduction cascades are uncoupled (Foreman *et al*., 1992; Smith, 1996; Ueyama *et al*., 1997). The adverse effects of GC and stress on neuronal homeostasis and their potential role as risk factors for AD will be further discussed in part III of this series.

THE HORMONES AND NEUROPEPTIDES ESTABLISH AN INTERACTIVE NETWORK

In the brain, neurotrophic agents establish a huge network of regulatory and effector functions in which CNS homeostasis is controlled by multiple feed forward and backward cycles. By this homeostatic network the optimal control of neuronal trophism, excitability, energy metabolism, Ca^{2+} and redox homeostasis is mediated. Control of glucose utilization, for example, is ensured by an integrated system consisting of insulin, NPY, IGFs, TH, neurotrophins, oestrogens, DHEA, SS, SP and GC. Mitochondrial efficiency is maintained by TH, NPY, neurotrophins, oestrogens, DHEA, IGF-1, and SP. Antioxidant homeostasis is regulated in concert by M, NGF, oestrogens, and DHEA. Neuronal Ca^{2+} homeostasis and excitability is controlled by TH, NPY, M, SS, IGFs, oestrogens, neurotrophins, DHEA and GC. Our insights into the cooperative control circuits is poor and at best bilateral interactions have been investigated. For instance, synergistic interactions and reciprocal regulations have been described for neurotrophins and TH, insulin and IGFs, oestrogens, NPY, SS and SP (Mill *et al*., 1985; Gibbs, 1994; Brewster *et al*., 1995; Carnahan and Nawa, 1995; Toran-Allerand, 1996; Fiumelli *et al*., 1997; Luesse *et al*., 1998), for oestrogen and TH, insulin, and IGF (Toran-Allerand *et al*., 1988; Freyschuss *et al*., 1994; Patrone *et al*., 1996; Shingo *et al*., 1997), and for TH and insulin/IGF-1 (Aizenman and de Vellis, 1987; Muller *et al*., 1991). There appears to be intensive colocalization, cross-talk, cross-coupling, substitution and counterregulation between signal transduction systems (Toran-Allerand *et al*., 1992; Dikic *et al*., 1994; Reinhardt *et al*., 1994; Brewster *et al*., 1995; Patrone *et al*., 1996; Guvakova and Surmacz, 1997). For instance, insulin and NGF elicit differential responses, although using the same cell signalling system. Overexpression of the insulin receptor leads to a more pronounced activation of its transduction system and allows insulin to mimic phenotypically the cellular actions of NGF (Dikic *et al*., 1994). Similarly, E2 can reverse the behavioural and hypometabolic effects of intracerebroventricular streptozotocin and thus, at least in part, substitute insulin (Lannert *et al*., 1998).

Neurotrophic/-protective and neuroaggressive agents inter- and counteract via multiple regulatory and effector mechanisms. Thereby, in a complex interplay, second messenger pathways converge in the regulation of effector functions, constantly integrating synergistic and antagonistic influences (Jehan *et al*., 1993). The antagonistic actions of GC and neurotrophins have been discussed earlier (Smith, 1996). DHEA has anti-glucocorticoid effects, in that it blocks GC synthesis and antagonizes a variety of glucocorticoid actions, particularly on learning and memory like fear conditioning (Kalimi *et al*., 1994; Fleshner *et al*., 1997). The suppression of GC synthesis might be regulated via the GABAergic action of DHEA on dorsomedial and paraventricular hypothalamic neurons (Bartanusz *et al*., 1995). However, in stress or serious illness, pregnenolone metabolism is shifted away from DHEA to GC. Gonadal hormones and GC show multiple, mostly antagonistic interactions. E and androgens interfere with glucocorticoid receptor function by reducing GC receptor message and impairing its feedback control (Burgess and Handa, 1992; Turner, 1997). Oral contraceptive users show blunted free cortisol responses to psychological and physical stress (Kirschbaum *et al*., 1995) and T inhibited HPA-responses to stress (Viau and Meaney, 1996). Stress and GC induce neuronal death in the hippocampus of castrated rats which can be blocked by substitution with T (Mizoguchi *et al*., 1992). M and GC establish a pineal–adrenocortical feedback cycle independent of the HPA-axis (Weidenfeld *et al*., 1993). Long-term stress induced M production in the rat (Milin *et al*., 1996). In human and rat, nighttime stress reduced M production while daytime stress increased M production (Monteleone *et al*., 1992). Pharmacological doses of GC, however, attenuated M production, whatever the circadian stage (Zhao and Touitou, 1993). Though inconsistent, the reported data suggest a functional, circadian modulated antagonism between M and GC. A role for M in the regulation of the stress response was also suggested by the finding that M acted as an anxiolytic in an animal conflict model (Naranjo-Rodriguez *et al*., 1995). SS secretions were inhibited by GC (Liu and Patel, 1995), and stimulated by T, while SS infusions in humans blunted the insulin-induced hypoglycemia-stimulated elevation of cortisol (Rubinow *et al*., 1995).

In the young CNS, the multiple neuroprotective agents outscore the neuroaggressive GC, maintaining a substantial safety margin and operational reserve which allow proper functioning even under adverse conditions. This delicately tuned, highly adaptable balance, however, is compromised during ageing.

AGEING AND HORMONAL BALANCE

Ageing is associated with the decline of a multitude of systemic and particularly tissue hormone levels and/or the deterioration of their signal transduction processes. This principle applies for a variety of cytoprotective hormones/peptides. In particular, the postreproductive period is characterized by a major change. In contrast, the activity of the HPA axis tends to increase. Ageing also leads to a disrupture of the diurnal and seasonal time structure of endocrinological rhythms (reviewed by Touitou and Haus, 1994). Our knowledge of CNS tissue neuropeptide/-hormone changes with ageing is still quite fragmentary. Data on brain specimen depend largely on animal studies where, due to genetically homogeneous samples, chronological age and biological ageing are more closely correlated, which allows more reliable conclusions from cross-sectional studies. In spite of these limitations, basic principles emerge, indicating that several neuroprotective factors decrease while neuroaggressive factors either remain stable or increase.

NPY levels are reduced in the human ageing brain (Arranz *et al*., 1996). Similarly, numbers of NPY immunoreactive cells gradually decrease in the ageing rat brain (Higuchi *et al*., 1991; Cha *et al*., 1996; Hugh *et al*., 1998; Zhang *et al*., 1998), despite an upregulation of NPY gene expression, indicating an accelerated turnover (Higuchi *et al*., 1991). The NPY decrease is possibly secondary to the degeneration of cholinergic neurons in the basal forebrain (Magni *et al*., 1998; Zhang *et al*., 1998). Functionally, this decline is accompanied by a reduced NPY responsiveness to fasting (Gruenewald *et al*., 1996).

After a peak in the early twenties, **DHEA** levels decay by about 20 per cent for every decade and reach only 10–15 per cent of the third decade level by the age of 85–90, paralleled by a loss of circadian rhythmicity (Bélanger *et al*., 1994; Sulcova *et al*., 1997; Nafziger *et al*., 1998). Likewise, DHEA sulfate levels undergo an ageing-related decrease and loss of circadian rhythm (Hornsby, 1995; Morley *et al*., 1997; Sulcova *et al*., 1997; Nafziger *et al*., 1998). The changes in plasma are paralleled by a concomitant decrease in

CSF (Guazzo *et al*., 1996). It is assumed that the decline of DHEA levels has a major impact on gonadal hormone levels as well. DHEA is converted in target organs into androgens and oestrogens and is the only source for oestrogen in postmenopausal women (Labrie *et al*., 1998). Low DHEAS levels in aged men may be predictors of death from any cause and particularly from cardiovascular disease (Barrett-Connor *et al*., 1986).

The temporal course of decline of **gonadal hormones** is different in human females and males (reviewed by Longcope, 1987). Women experience a complete and abrupt cessation of ovarian function during menopause, resulting in a dramatic decline of E levels. Thereafter, the concentrations remain constant at a low level. The major source of circulating E then becomes the peripheral conversion of androgens by aromatization. The female brain reflects the peripheral decrease of E concentrations (Bixo *et al*., 1995), and the age-related decrease of synaptic markers in the rat appears to be related to the level of E rather than GC (Chao *et al*., 1996). Ovarian factors other than E are necessary for the maintenance of DHEA levels. Premature ovarian failure and ovariectomy precipitate an earlier DHEA decline which did not respond to oestrogen replacement therapy (Cumming *et al*., 1982). In ageing men, the secretion and circulating levels of T decline gradually, with the major decrease occurring after the age of 60 (Deslypere and Vermeulen, 1984). Older men have decreased levels of luteinizing hormone (LH) and T (Mitchell *et al*., 1995; Morley *et al*., 1997). The decrease of T is associated with an increase of sex hormone binding globulin, resulting in a marked decline of free, biologically active T (Deslypere and Vermeulen, 1984). In the brain, T is converted to E2 by aromatization which may underly the good correlation of bioavailable T with cognition in elderly men (Morley *et al*., 1997). However, brain T binding and metabolism in old rats was reported to be deficient (Chambers *et al*., 1991). Moreover, in ageing rats brain E2 receptors are decreased (Kanungo *et al*., 1975).

Plasma **melatonin** levels decline with age in humans and rodents, the reduction being apparent both in the circadian and seasonal mean levels and particularly the nocturnal peak (Reiter *et al*., 1980; Touitou *et al*., 1984). These findings were confirmed by CSF and urinary metabolite levels (Brown *et al*., 1979; Liu *et al*., 1999). The age-related decline of M biosynthesis (Humbert and Pevet, 1994) is possibly Ca^{2+} mediated, which is evidence for another feedback loop (Schmid, 1993).

The activity of GH-**IGF axis** undergoes an age-related decrease (Cohen *et al*., 1992). In the elderly both spontaneous and GH-releasing hormone-stimulated GH secretion and IGF levels are frequently low (Ghigo *et al*., 1996; Rollero *et al*., 1998). Moreover, the ratio of IGF-1 to growth hormone decreases, indicating a reduced responsiveness (Morley *et al*., 1997). In the third or fourth decade of life, tissue responsiveness to insulin is progressively deteriorating, characterized by a reduced glucose tolerance and increased fasting insulin levels (DeFronzo, 1981; Pagano *et al*., 1984). In the human brain, levels of insulin, insulin receptors, and activity of the signal transducing tyrosine receptor kinase decrease with advancing age, while IGF-1 receptors are unchanged (De Keyser *et al*., 1994; Frölich *et al*., 1998). In aged rats, low serum levels of IGF-1 were associated with reduced brain IGF-1, IGF-1 mRNA and IGF-1 receptor levels (Lopez-Fernandez *et al*., 1996; Sonntag *et al*., 1998). Likewise, brain IGF-2 mRNA levels were reduced (Kitraki *et al*., 1993). Plasma IGF-1 levels correlated with cognitive performance in humans (Rollero *et al*., 1998), corroborating the importance of IGF for CNS functionality. Moreover, IGF-1 signal transduction is impaired, resulting in an attenuated stimulation of protein synthesis in aged rat cerebral cortex (D'Costa *et al*., 1995; Renganathan *et al*., 1997). Putatively reflecting the cellular stress role of IGF receptors (see above), IGF-1 receptor mRNA in aged rat hippocampus was increased, correlating with cognitive decline (Stenvers *et al*., 1996). However, these changes were not reflected at the level of the translated protein (Dore *et al*., 1997). Given the important role of GH and IGF-1 in vascular maintenance and remodelling, the decrease of both hormones has been related to the decrease of cortical arteriolar density and could be reversed by hormone supplementation (Sonntag *et al*., 1997). Moreover, since the vasculature is an important source of IGF-1 for the brain (Sonntag *et al*., 1998), the degeneration of the cerebral vasculature and impaired blood–brain-barrier transport may contribute significantly to the age-related cerebral IGF deficit.

Levels of **somatostatin** and SS mRNA were decreased in ageing rodent brain (Unger and Schmidt, 1994; Zhang *et al*., 1998), and in ageing primate brain (Hayashi *et al*., 1997). The reduction

of SS mRNA levels in the ageing rodent frontal and parietal cortex correlated with cognitive impairment (Dournaud *et al*., 1996) and may be secondary to the degeneration of cholinergic basal forebrain neurons (Zhang *et al*., 1998).

Cortical and hippocampal **NGF** levels remain unchanged during ageing in the human and rat brain (Kerwin *et al*., 1993). NGF receptor levels, however, were found to be decreased in the basal forebrain (Hefti and Mash, 1989; Markram and Segal, 1990; Ma *et al*., 1998) and the loss of trkA levels correlated with the *ante mortem* cognitive impairment (Ma *et al*., 1998). The levels of BDNF mRNA were decreased in ageing primate brain (Hayashi *et al*., 1997). In rodents, ageing is associated with reduced NGF and trkA mRNA levels in the basal forebrain (Koh and Loy, 1988; Gomez-Pinilla *et al*., 1989; Cooper *et al*., 1994). The hippocampus showed either no changes (Crutcher and Weingartner, 1991), or reduced hippocampal NGF content (Larkfors *et al*., 1987; Henriksson *et al*., 1992) and the reduction correlated with cognitive impairment (Henriksson *et al*., 1992). On the other hand, hippocampal NGF and BDNF mRNA levels were found elevated, also correlating with cognitive decline (Sugaya *et al*., 1998). An ageing-related reduction of retrograde transport of NGF from the hippocampus and cortex to the basal forebrain (Cooper *et al*., 1994; De Lacalle *et al*., 1996) may trigger the degenerative changes of basal forebrain cholinergic neurons. Moreover, NGF may lose its capacity to regulate neuronal Ca^{2+} homeostasis (Itoh *et al*., 1998).

Indices of the hypothalamic–pituitary–thyroid axis function in ageing individuals indicate a high incidence of **thyroid hormone** deficiencies with normal or increased serum TSH, decreased stimulated TSH secretion, decreased sensitivity of the thyroid gland to TSH, impaired feedback control of T3 on pituitary thyrotrophs, decreased productive or releasing capacities of the thyroid gland and decreasing serum levels of T3 in ageing man, monkey and rat (Hesch *et al*., 1976; Harman *et al*., 1984; Drinka and Nolten, 1988; Monzani *et al*., 1996). T4 and T3 production rates are decreased in older rats and did not increase during overfeeding as observed in young adult rats (Katzeff, 1990). Even more than the periphery, the ageing brain is in a functional hypothyroid state. Blood–brain transport of T3 is reduced in aged rats; however, this decline is counterbalanced by a decreased T3 clearance from the brain (Mooradian, 1990). During ageing the mRNA level, the binding capacity and affinity of rodent brain T3 nuclear receptors, as well as T4 binding, declines (Margarity *et al*., 1985; Enderlin *et al*., 1997), which results in a reduced responsiveness of cerebral tissue to TH (Mooradian *et al*., 1998). Furthermore, activity of the deiodinase which converts T4 to T3 is reduced in liver and brain (Margarity *et al*., 1985). Since the thyroxine deiodinase activity appears to be regulated by the glutathione and NADPH redox equilibrium (Sato and Robbins, 1984), this may represent another indicator of increased oxidative stress in the ageing brain (see below). That during ageing, the brain suffers from a relative TH deficit is indicated by the ageing-related increase of CSF transthyretin (Serot *et al*., 1997), suggesting a compensatory upregulation of the neuronally controlled choroid plexus production (Nilsson *et al*., 1992).

Human CSF levels of **SP** decrease with increasing age (Cramer *et al*., 1985); in the brain tissue, however, only the putamen showed a significant age-related SP level decrease (Buck *et al*., 1981).

In a variety of cross-sectional studies in healthy elderlies, basal **glucocorticoid** levels were not altered (e.g. Huizenga *et al*., 1998), while in others they were (e.g. Touitou *et al*., 1983; Pavlov *et al*., 1986; Deuschle *et al*., 1997), particularly in one study involving more than 2000 men (Bélanger *et al*., 1994). More consistently, during nighttime sleep the HPA axis exhibited an increased secretory activity, and a dampening of circadian and circannual rhythmicity and loss of feedback inhibition correlating with age and cognitive impairment (Touitou *et al*., 1983; Van Cauter *et al*., 1996; Deuschle *et al*., 1997; Magri *et al*., 1997). Moreover, in normal aged compared to young humans, the HPA axis displays both an increased sensitivity to stressors and activity under challenge (Dodt *et al*., 1991; Gotthardt *et al*., 1995; Raskind *et al*., 1995), and impaired feedback regulation (Pavlov *et al*., 1986; Dodt *et al*., 1991; O'Brien *et al*., 1994). Overall, these changes result in a significant increase of mean plasma GC levels in elderlies (Van Cauter *et al*., 1996). Likewise, cortisol levels are increased in elderly ventricular and lumbar CSF (Swaab *et al*., 1994; Guazzo *et al*., 1996). A longitudinal study in healthy elderly subjects revealed divergent basal and diurnal cortisol levels among subgroups (Lupien *et al*., 1996). Higher levels predicted worse cognitive performance (Lupien *et al*., 1994,

1998), hippocampal atrophy (Lupien *et al*., 1998), higher stimulated cortisol levels and cognitive impairment in response to stressors (Meaney *et al*., 1995). Another study correlated elevated basal GC with cognitive impairment and defective feedback inhibition with cognitive decline (Kalmijn *et al*., 1998). Similarly, in elderly women but not in men, an increased urinary cortisol excretion was associated with poor baseline memory performance and cognitive decline on follow-up (Seeman *et al*., 1997). In animals, ageing enhances the basal activity of the HPA axis and perturbs the HPA responsivity (DeKosky *et al*., 1984; Oxenkrug *et al*., 1984; Meaney *et al*., 1992; Hatzinger *et al*., 1996) which correlated with cognitive impairment (Issa *et al*., 1990). Since corticosterone circadian rhythms and levels were equally abnormal in aged and pinealectomized rats, a causal relationship between fall of M and rise of GC levels has been suggested (Oxenkrug *et al*., 1984). Furthermore, GC in response to a stressor is increased and the recovery of GC levels is impaired (Sapolsky *et al*., 1983; Issa *et al*., 1990; van Eekelen *et al*., 1992). In addition, concentrations of GC binding globulin are decreased, thus augmenting the amount of free GC (Meaney *et al*., 1992; van Eekelen *et al*., 1992). Likewise, in elderly compared with young humans, an increase of the active free fraction of plasma cortisol was observed (Touitou *et al*., 1982; 1983), a finding which was not confirmed in another study (Pavlov *et al*., 1986). A causal relationship of the increased activity of the HPA axis with ageing has been suggested. The 'glucocorticoid cascade hypothesis' of stress and ageing (Landfield, 1978; Sapolsky *et al*., 1986) conceptualized the findings that (1) plasma GC levels correlate with hippocampal ageing; (2) adrenalectomy protects against features of hippocampal ageing; (3) and long-term stress and GC administration elicit premature development of hippocampal ageing and has been expanded later (reviewed by Landfield and Eldridge, 1994; Smith, 1996; McEwen, 1999, see part III of this series).

There may be other neurohormones/-peptides with pathophysiological roles in AD. However, since for the time being their contribution to the neuroprotective/-aggressive balance cannot properly be assessed, they have been omitted. Others with putative roles in the pathophysiological process, e.g. corticotrophin-releasing factor, vasopressin and galanine, will be discussed later.

CONSEQUENCES OF THE IMPAIRED HORMONAL BALANCE FOR THE CALCIUM–ENERGY–REDOX TRIANGLE

The loss of hormonal balance impairs the Ca^{2+} handling capacity of neurons, puts them under metabolic and oxidative stress and increases their vulnerability to a variety of noxious stimuli.

Ageing and calcium homeostasis

The review of the data on calcium homeostasis in the ageing brain obtained in a wealth of animal studies faces a profound inconsistency of reported ageing-related alterations (Peterson, 1992). Use of different animal species and strains and neuronal cell populations may in part account for the inhomogeneity of the results. The main source of variability, however, probably is due to dynamic Ca^{2+} shifts induced by traumatic homogenization and fractionation methods, uncontrollably activating Ca^{2+} redistributions (Meldolesi *et al*., 1988). It has been shown that even mild traumatic deformations induce Ca^{2+} perturbations and membrane permeability changes (Tavalin *et al*., 1995; LaPlaca and Thibault, 1998), aged neurons being mechanically more vulnerable compared to young ones (Hamm *et al*., 1992; Johnson and Duberley, 1998). To integrate the conflicting data into a coherent picture, choices have to be made. These choices should not be arbitrary, but should depend on the degree of intactness of the tissue from which the data have been generated. Thus, *in vivo* and *in situ* data clearly should be weighted more than data obtained with homogenized tissues and in culture experiments.

Keeping in mind the limitations of the presented data, the ageing brain cells exhibit a multitude of deficiencies in Ca^{2+}-related events and maintenance of Ca^{2+} homeostasis, creating a plethora of dysregulated processes in neuroplasticity and structural maintenance (for reviews see Peterson, 1992; Disterhoft *et al*., 1994; Landfield, 1994; Verkhratsky and Toescu, 1998).

In vivo and *in vitro* data suggest the intracellular accumulation of Ca^{2+} in aged rat brain (Das and Ghosh, 1996; Kirischuk and Verkhratsky, 1996; Satrustegui *et al*., 1996; Verkhratsky *et al*., 1996). In aged rat hippocampal neurons, synaptic plasticity was impaired, apparently due to a variety of excessive Ca^{2+} currents and a substantial increase of L-type Ca^{2+} channel density (Landfield, 1996) which correlated with learning disability (Thibault

and Landfield, 1996). Similarly, 'ageing' of hippocampal neurons in culture increased L-type Ca^{2+}-channel density due to a change in gene expression (Porter *et al*., 1997). Both voltage-gated and receptor-operated Ca^{2+} channels such as NMDA channels were found elevated in the hippocampus (Araki *et al*., 1993), and evidence suggested that the Mg^{2+} block of NMDA receptors is attenuated (Okada *et al*., 1992). Accordingly, stimulus-evoked Ca^{2+} signals were found prolonged (Kirischuk and Verkhratsky, 1996), whole-cell Ca^{2+} currents were increased in senescent neurons due to a greater channel activity (Campbell *et al*., 1996), and neuronal excitability reduced (Cepeda *et al*., 1992; Potier *et al*., 1992). The recovery of Ca^{2+} to the basal level after depolarization-related elevation was much slower in aged neurons, which could lead to elevated mean Ca^{2+} levels upon neuronal activity (Verkhratsky *et al*., 1996). In contrast, aged dorsal root ganglion cells showed a decreased voltage-induced Ca^{2+} influx and reduced number of active Ca^{2+} channels (Verkhratsky *et al*., 1996). Noteworthy strikingly similar, albeit regionally differential (Denisova *et al*., 1997) changes, together with a reduction of ATP and [ATP]\[ADP] ratio, could be induced in neural cells and synaptosomes by oxidative stress: increase of baseline Ca^{2+} levels, decreased stimulated rise of Ca^{2+}, and reduced ability to extrude excess Ca^{2+} resulting in prolonged recovery times (Joseph *et al*., 1997; Tretter *et al*., 1997). In other experimental systems, Ca^{2+} influx was reportedly diminished in senile neurons (Hartmann *et al*., 1996). The aged rat brain exhibited a dramatic reduction of Ca^{2+} binding proteins, namely of calbindin and calretinin in hippocampal pyramidal neurons (Villa *et al*., 1994; De Jong *et al*., 1996), and of parvalbumin in the medial septal area and cingulate cortex (Krzywkowski *et al*., 1996). Likewise, ageing causes selective loss of calbindin from the cholinergic neurons of the human basal forebrain (Iacopino and Christakos, 1990; Wu *et al*., 1997; Geula *et al*., 1998). The smooth endoplasmic reticulum (ER) Ca^{2+} buffering capacity declines in senescence, rendering the neurons more reliant on mitochondrial Ca^{2+} buffering (Tsai *et al*., 1998). This may be related to a marked accumulation of Ca^{2+} in the aged ER under resting conditions, while this intracellular store has only a reduced capacity of sequestration under activity (Verkhratsky *et al*., 1996; Tsai *et al*., 1998, see below). In addition, Ca^{2+} compartmentation and buffering capacity in synaptosomal mitochondria is also reduced due to a decrease in activity of the mitochondrial Ca^{2+} uniporter (Vitorica and Satrustegui, 1986; Satrustegui *et al*., 1996) and the latter together with decreased mitochondrial Ca^{2+} content was correlated with impaired cognitive performance (Huidobro *et al*., 1993; Blanco *et al*., 1994). The reduced mitochondrial Ca^{2+} uptake may be secondary to a compromised energy metabolism (Padua *et al*., 1998), a feature which further highlights the intricate and reciprocal interrelationship of Ca^{2+} and energy homeostasis. On the other hand, in ageing the plasmalemmal Ca^{2+} export declines due to a decreased activity of both the Ca^{2+}-ATPase and Na^{+}-Ca^{2+} exchanger (Canzoniero *et al*., 1992; Michaelis *et al*., 1996; Gao *et al*., 1998). These findings are in line with another set of experiments showing that membrane composition and structure are altered in ageing, resulting in a decreased activity of the Ca^{2+}-ATPase (discussed in part III of this series). Finally, calmodulin, which is part of the government circuitry of the cell, integrating and coordinating the Ca^{2+} currents (Williams, 1992), is decreased by about 50 per cent in the ageing brain (Teolato *et al*., 1983). Moreover, calmodulin is oxidatively modified and displays a reduced ability to activate Ca^{2+}-dependent processes, e.g. the Ca^{2+}-ATPase (Michaelis *et al*., 1996; Gao *et al*., 1998). Thus, reduced Ca^{2+} buffering by mitochondria, ER and binding proteins and extrusion capacities for Ca^{2+} may synergize to effect the observed Ca^{2+} basal level alterations, handling defects and increasing inability to cope with Ca^{2+} loads of aged neurons (Hanahisa and Yamaguchi, 1997).

Ageing and energy homeostasis

Ageing is associated with changes in regional cerebral blood flow and diminished oxygen and glucose metabolism. Deficits in speed of visual perception and accuracy of recognition were associated with a reduced activation of critical brain areas accompanied by activation of other areas indicative of compensatory changes in elderly compared with young humans (Grady, 1996). Age-related reductions of regional cerebral blood flow (Waldemar, 1995; Akiyama *et al*., 1997; Claus *et al*., 1998) and cerebral oxygen metabolism at rest and during brain activation have been demonstrated (Marchal *et al*., 1992; Hock *et al*., 1996). In human, parietal, frontal and prestriate cortices exhibited a decreased glucose metabolism averaging a 6–8 per

cent decline per decade (Hoyer, 1994; Blesa *et al*., 1997; Petit-Taboue *et al*., 1998), correlating with cognitive impairments (Gage *et al*., 1984; Riege *et al*., 1985). In the medial temporal lobe more than in the frontal lobe, indices of metabolic activity were reduced age-dependently upon magnetic resonance spectroscopy in normal elderlies (Fukuzako *et al*., 1997). *In vitro* use of glucose by senescent human brain neurons is progressively decreased (Swerdlow *et al*., 1993). Likewise, significant reductions of glucose utilization were noted in the rat (Tack *et al*., 1989; Nakayama and Nagai, 1997).

There is substantial evidence that mitochondrial function declines with age. The age-dependent deficits manifest in an impaired mitochondrial handling of Ca^{2+}, an increased release of ROS and level of oxidative damage to mitochondrial DNA, a reduced ability to comply with the cellular energetic demand and increased susceptibility to mitochondrial inhibitors. Senescent rat hippocampal neurons and human cerebellum exhibit a reduced density of mitochondria, while the volume of mitochondria increases presumably as a compensatory response (Bertoni-Freddari *et al*., 1996, 1997). Ca^{2+} uptake through the mitochondrial uniporter declines with age, while the steady state Ca^{2+} distribution across the mitochondrial membrane is shifted towards higher cytosolic Ca^{2+} levels and the mitochondrial Ca^{2+} buffering capacity decreases (Vitorica and Satrustegui, 1986). Recently, the repercussions of mitochondrial Ca^{2+}/energy compromise on ER Ca^{2+} homeostasis have been demonstrated, the former leading to impaired ER Ca^{2+} release and uptake (Landolfi *et al*., 1998). In ageing rodent and primate brain, energy production may be less effective, even deficient in response to metabolic stress (Bertoni-Freddari *et al*., 1996), due to an impaired mitochondrial glucose oxidation and oxidative phosphorylation (Bowling *et al*., 1993; Ferrandiz *et al*., 1994), a decline of cytochrome oxidase activity (Curti *et al*., 1990; Sohal, 1993), and a reduced Ca^{2+}-mediated activation of pyruvate dehydrogenase (Bogonez *et al*., 1992). Moreover, ROS release of mitochondria increases with ageing (Sohal and Sohal, 1991), and presumably as a consequence of oxidative stress the electron transport chain has a lower activity and induction of the mitochondrial PT is enhanced (Zhang *et al*., 1990; Goodell and Cortopassi, 1998). Consequently, older animals exhibited a greater susceptibility to anoxia and neurotoxic substances causing mitochondrial dysfunction (Beal *et al*., 1993; Roberts and Chih, 1995). The relationship of these metabolic deficits to cognitive impairment was suggested by the correlation of impaired glucose metabolism and learning deficits in senescence-accelerated mice (Ohta *et al*., 1996).

Various studies demonstrated age-dependent reductions of mitochondrial gene expression (Petruzzella *et al*., 1992), increases in mitochondrial deletions, mitochondrial point mutations, and oxidative damage to DNA (reviewed by Beal, 1995). The brain tissue is particularly vulnerable due to its postmitotic state, allowing the DNA damage to accumulate over time (Cortopassi and Arnheim, 1990) and its active Ca^{2+} and energy turnover exposing the mtDNA to high oxidative stress. Moreover, mtDNA has only limited repair mechanisms, is not protected by histones and is close to the inner membrane where ROS are produced (Clayton *et al*., 1974; Richter *et al*., 1988; Shigenaga *et al*., 1994). Thus, the age-related increase of oxidative damage of brain DNA is more prevalent in mitochondrial than nuclear DNA (Mecocci *et al*., 1993). Furthermore, mtDNA deletions increase with ageing in various tissues, including the brain of humans and other species (Cortopassi and Arnheim, 1990; Corral-Debrinski *et al*., 1992), again correlating with features of oxidative stress (Wei *et al*., 1996). Mitochondrial proteins exhibit an ageing-associated gradual increase of carbonyl content suggestive of accumulating exposure to oxidative stress (Martinez *et al*., 1996). A further link is provided by the finding that in senescent human muscle, high levels of mutant mtDNA correlated with low cytochrome c oxidase activity (Brierley *et al*., 1998). Finally, a reduction of mitochondrial membrane fluidity was observed along with age and correlated with another marker of oxidative stress, the content of oxidized nucleotides in mtDNA (Mecocci *et al*., 1997). It has been suggested that these mitochondrial defects are causal to ageing (Harman, 1972; Wallace, 1992; Shigenaga *et al*., 1994). The concomitant action of ageing-related energetic stress and mitochondrial defects reduces the adaptive reserve of neurons and renders them vulnerable to a variety of stressors, such as glutamate and corticosteroids (Brewer, 1997). The energy-vulnerability interdependence was further epitomized by the finding that cells with a high energy demand are more sensitive to mitochondrial impairment (Erecinska and Nelson, 1994).

Ageing and redox homeostasis

The mitochondrial respiratory chain reduces oxygen (O_2) to water (H_2O) through the addition of four electrons and four hydrogen atoms. The cascade of reactions involves the formation of ROS, the superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^\bullet$). Other ROS are generated during the enzymatic pathways of xanthine oxidase, aldehyde oxidase, cytochrome P-450 complex, and phospholipase A_2. Intriguingly, most of these enzyme activities are under Ca^{2+} control. On the other hand, evolution has equipped the cells with various enzymatic (superoxide dismutase [SOD], catalase, glutathione peroxidase) and non-enzymatic (vitamins C and E, β-carotene, and thiols such as glutathione) antioxidant defence mechanisms to keep the oxidative threat to the cellular homeostasis at bay. Oxidative stress may occur when either the generation of ROS is increased or antioxidative mechanisms are deficient. In ageing, the balance of prooxidant and antioxidant agents is compromised (Benzi and Moretti, 1995). As outlined above, dysregulated Ca^{2+} and energy homeostasis may convert mitochondria into virtually inexhaustible ROS generators. Consequently, during ageing mitochondrial ROS generation increases (Sohal and Sohal, 1991; Sawada *et al*., 1992; Gabbita *et al*., 1997). Moreover, the physiological function of mitochondria as scavenger of extramitochondrial ROS (Guidot *et al*., 1995) may be lost.

Thus, ageing is associated with and may even be dependent on a variety of oxidative reactions of nucleic acids, proteins and lipids (reviewed by Harman, 1992). The brain is particularly susceptible to oxidative damage due to its high oxygen consumption rate, relatively low level of antioxidant enzymes, regionally high iron levels and high lipid content, particularly rich in polyunsaturated fatty acids (Coyle and Puttfarcken, 1993). The competence of the antioxidant defence decreases and concomitantly ROS and oxidation products increase in ageing rodent and human brain (Chen *et al*., 1989; Smith *et al*., 1991; de la Asuncion *et al*., 1986; O'Donnell and Lynch, 1998; reviewed by Ceballos-Picot, 1997). Thus in comparison to young controls, the ageing brain has impaired compensatory antioxidant mechanisms (Chang *et al*., 1995), and hence is more susceptible to oxidative stress-induced necrosis and apoptosis (Adams *et al*., 1996; Jurma *et al*., 1997). Glutathione in its reduced and oxidized state (the GSH-GSSG system) plays a pivotal role in cellular redox homeostasis (Ceballos-Picot, 1997). Notably, GSH decreases in cortex and hippocampus (Chen *et al*., 1989; Ravindranath *et al*., 1989), while mitochondrial glutathione oxidation increases and correlates with oxidative damage to mtDNA (de la Asuncion *et al*., 1996; Ceballos-Picot, 1997). Moreover, the decrease of hippocampal SOD was a marker of impaired cognitive performance in aged rats (Sugaya *et al*., 1996). Glycation of proteins also indicates oxidative stress. Advanced glycation end products (AGE) result from a post-translational, non-enzymatic condensation of amino groups of proteins with reducing sugars in the Maillard reaction. Glycation and oxidation mutually affect each other in a synergistic and additive way (Hunt *et al*., 1988; Mullarkey *et al*., 1990; Odetti *et al*., 1994). Overall, modification of proteins by glycoxidation AGE products accumulate with age in human hippocampal neurons (Kimura *et al*., 1996; Takeda *et al*., 1996). Lipofuscins are another marker of ageing-related oxidative stress. Lipofuscin is an intracellular autofluorescent pigment which accumulates in the cerebral and other tissues in a linear correlation with ageing (Dowson, 1982). Although the exact chemical nature of the deposits is not known, one component is lipid peroxidation products (Jolly *et al*., 1993). Moreover, lipofuscins also consist of AGE adducts (Horie *et al*., 1997). Circumstantial evidence indicating a reciprocal relationship of antioxidant and lipofuscin levels highlight the role of oxidative stress in the process of lipofuscin accumulation (Dowson *et al*., 1992; Lopez-Torres *et al*., 1993; Gao *et al*., 1994). Thus, lipofuscins can be regarded as oxidative stress-derived lipid, carbohydrate and protein condensation polymers.

AGEING AND ORGAN FUNCTIONS

Ageing and neuronal plasticity

Neuronal plasticity can be defined as the ability of the nervous system to change its structure and function following either experience (resulting in learning and memory-related behavioural modifications) or injury. Evidence exists for impaired plasticity of neurons in the aged brain, which leads to a decreased ability for adaptive changes, decrements of learning and memory and behavioural slowing (reviewed by Verhaeghen *et al*., 1993; Birren and Fisher, 1995).

Both in autopsy specimens and structural neuroimaging studies, a cerebral atrophy and loss of neurons with increasing age has been suggested (Terry *et al*., 1987; Kaye *et al*., 1997). Importantly for cognitive processes, the shrinkage and neuronal loss was more pronounced in the association cortex compared to primary cortex (Kemper, 1984; Haug and Eggers, 1991), in the prefrontal cortex (estimated linear decline of approx. 5 per cent per decade) (Raz *et al*., 1998), and in medial temporal regions, including subdivisions of the hippocampus (Jack *et al*., 1998; Raz *et al*., 1998). More accurate stereological procedures for counting neurons not relying on neuron density in a given structure, however, indicated that neuronal loss is not a prerequisite for the functional deficits in normal ageing (reviewed by Mrak *et al*., 1997; Morrison and Hof, 1997). In healthy humans, nonhuman primates and rodents evolution of synaptic pathology is an early marker of ageing (Greenough *et al*., 1978; Agnati *et al*., 1992; Martin *et al*., 1994) and precedes the formation of amyloid deposits in the primate brain (Martin *et al*., 1994). Dendritic neuropil declines with age, particularly with regard to spine number and density which, in particular brain regions, may decrease by almost 50 per cent (Anderson and Rutledge, 1996; Jacobs *et al*., 1997). Likewise, a marker for dendritic plasticity, drebrin, is decreased with ageing in the human cortex (Hatanpää *et al*., 1997). The loss of synaptic connections correlates with the decline of cognitive performance in ageing rats (Wong *et al*., 1998). Dendritic extent, on the other hand, is quite variable depending upon the region, species and age range studied (Coleman and Flood, 1987). An ageing-related increase of dendritic extent, particularly in the hippocampus, can be interpreted as an adaptive, compensatory response to loss of synaptic connections (Flood and Coleman, 1990). These region- and age range-specific dendritic alterations seem to correlate with lifespan alterations in volume of pertinent brain regions (Uylings *et al*., 1998). An axonal pathology is reflected by a diminished axonal transport (Geinisman *et al*., 1977), decreased neurofilament gene expression (Kuchel *et al*., 1996) and a loss of soluble tau which amounts to 14 per cent per decade and may even reach levels of 90 per cent in frontal cortex and hippocampus (Mukaetova-Ladinska *et al*., 1996). In addition, ageing alters distribution profiles of distinct tau isoforms, presumably due to hyperphosphorylation and fragmentation events (Bahr and Vicente, 1998).

During ageing, the decrease in spine density is paralleled by impairment of various electrophysiological parameters of short-term synaptic plasticity (Ou *et al*., 1997). Electrophysiological features of synaptic transmission and LTP are also impaired, exhibiting a selective pattern of degenerative changes and functional sparing (Landfield and Pitler, 1984; Barnes, 1994; Foster and Norris, 1997; Shankar *et al*., 1998) associated with a compromise of the LTP-related transcriptional response (Lanahan *et al*., 1997) and synaptogenesis (Chang *et al*., 1991; Geinisman *et al*., 1994). The electrophysiological changes seem to be mediated by a shift from NMDA-dependent to voltage-dependent L-type Ca^{2+} channel mechanisms (Shankar *et al*., 1998) and can be ameliorated by L-type Ca^{2+} channel blockade (Araki *et al*., 1997; Norris *et al*., 1998). Moreover, neuronal Na^{+},K^{+}-ATPase expression is decreased in the ageing brain (Chauhan *et al*., 1997) with potentially adverse effects on membrane potential and neuronal excitability. In the interplay of these factors, the synaptoplastic potential of the ageing brain is decreased, the axonal sprouting delayed and less effective in forming new and replacing lost connections (McWilliams and Lynch, 1984; Anderson *et al*., 1986). Finally, in ageing rats cerebral angiogenesis is impaired progressively, failing to support neuronal plasticity (Black *et al*., 1989; Sonntag *et al*., 1997).

Ageing is associated with alterations of various neurotransmitter systems. Glucose-derived neurotransmitters are generally decreased in the ageing rodent brain (Gibson *et al*., 1981). The cholinergic system is important in learning and memory and its function declines with normal ageing (reviewed by Taylor and Griffith, 1993; Geula and Mesulam, 1994; Muir, 1997). Consistently, age-related deficits were documented for conduction latencies in cholinergic basalocortical projections, ChAT in a brain region-specific pattern, cholinergic terminal integrity, ACh turnover, ACh synthesis, stimulated ACh release, cortical and hippocampal ACh levels, nicotinic (up to −80 per cent), but not muscarinic, cholinergic receptors and subunits, cholinergic signal transduction, and adaptive receptor plasticity. The loss of basal forebrain cholinergic neurons correlated with the loss of calbindin (Geula *et al*., 1998). Moreover, the degeneration of cholinergic basal forebrain neurons correlated with a decline of retrograde axonal transport (De Lacalle *et al*., 1996). Remarkably, cholinergic fibre loss was associated with occurrence of diffuse

plaques, constituting a potential preclinical stage of AD (Beach *et al*., 1997). *In vivo*, the ageing-related cholinergic dysfunction is epitomized by an increased sensitivity of cognitive functions to muscarinergic inhibition (Tariot *et al*., 1996).

Additional degenerations of the serotonergic, catecholaminergic and glutamatergic systems may aggravate the cognitive deficits. The serotonergic (5-HT) system cooperates with the cholinergic system in the maintenance of cognitive functions (Cassel and Jeltsch, 1995). 5-HT1 and 2 receptor densities and signal transduction processes decline in human, primate and rat cortex and hippocampus; the levels of 5-HT decrease in nonhuman primates and remain stable in human and rat, while the 5-HT turnover increases (reviewed by Morgan, 1987; McEntee and Crook, 1991; Richter-Levin and Segal, 1996). Noradrenergic (NA) functions decline with ageing, adrenergic receptor densities and plasticity are reduced in selected brain regions and signal transduction mechanisms are impaired (Olpe and Steinmann, 1982; Greenberg, 1986; Scarpace and Abrass, 1988). On the other hand, cell density in the NA nucleus coeruleus appears not to be reduced (Ohm *et al*., 1997). A loss of dopaminergic D2 receptors has been shown *in vivo* and postmortem in humans, monkeys, and rodents, paralleled by a decrease of dopamine content and turnover, indicating the degeneration of the nigrostriatal system (Severson *et al*., 1982; Wong *et al*., 1984). Finally, the glutamatergic system undergoes an age-related modification. The direction, brain region-, receptor subgroup- and species specificity, and the functional consequences of these changes, however, appear highly variable, are so far only fragmentarily defined and await further clarification. NMDA receptor densities decline in various brain regions of ageing monkeys and rodents (Wenk *et al*., 1991; Ingram *et al*., 1992; Gazzaley *et al*., 1996; Le Jeune *et al*., 1996). In human brain either no (Johnson *et al*., 1996) or a significant decline in the frontal cortex were reported (Piggott *et al*., 1992). On the other hand, the NMDA receptor deficits seem to be compensated functionally and electrophysiologically (Serra *et al*., 1994; Billard *et al*., 1997). AMPA receptor densities were reported either increased, unchanged or reduced in rat hippocampal subfields (Miyoshi *et al*., 1991; Le Jeune *et al*., 1996; Nicolle *et al*., 1996). Importantly, age-related changes in expression of AMPA receptor subunits in the hippocampus and basal forebrain may have detrimental consequences for neuronal vulnerability due to altered Ca^{2+} permeability (Pagliusi *et al*., 1994; Akaike and Rhee, 1997). Overall, evidence on the behavioural consequences of glutamatergic receptor imbalances is patchy and inconsistent. The NMDA receptor deficits were either associated with impaired (Müller *et al*., 1994; Magnusson, 1998) or improved cognitive performance (Le Jeune *et al*., 1996; Nicolle *et al*., 1996), while hippocampal AMPA receptor upregulation was correlated with worse memory (Le Jeune *et al*., 1996), but facilitation of AMPAergic transmission improved memory (Granger *et al*., 1996).

Due to the importance of Ca^{2+} for neuronal plasticity (Mattson, 1992; Teyler *et al*., 1994; Ghosh and Greenberg, 1995), it can be regarded as a concatenation of the ageing-related compromise of Ca^{2+} homeostasis that synaptic plasticity in ageing is disrupted as well (Foster and Norris, 1997). In addition, other signal transduction pathways were found impaired in aged human and rodent brain involving G-proteins, adenylate cyclase, inositol polyphosphates, and PKC (reviewed by Joseph *et al*., 1993; Fülöp and Seres, 1994; Sugawa *et al*., 1996). The impaired neuronal plasticity was associated with an ageing-related decline in DNA transcription, protein levels and biomembranes (Sugawa *et al*., 1996; Sugaya *et al*., 1996; Lee *et al*., 1998), changes which may be related to oxidative stress (Joseph *et al*., 1996).

Finally, given the paramount role of astroglial cells for neuronal function and integrity (reviewed by Vernadakis, 1996), the closely age-related increase of an astroglial activation marker, glial fibrillary acidic protein (GFAP), indicates that astroglia in the ageing brain and particularly the hippocampus and isocortex, are also exposed to increasingly stressful conditions (Nichols *et al*., 1993; David *et al*., 1997), which may potentially adversely effect their support of neuronal synaptogenesis and synaptic transmission (Keyser and Pellmar, 1994; Nakanishi *et al*., 1994; reviewed by Vernadakis, 1996).

Ageing and immune system

Two functional systems mediate the immune responses: (i) innate immunity, a host defence system already present in primitive life, characterized by unspecific cellular and humoral effectors; and (ii) adaptive immunity, an antigen-specific, genetically restricted, memory-endowed cellular and humoral system. Primary carriers of the innate system are the phagocytes of the

monocyte/macrophage and polymorph lineages and the complement system; the adaptive system relies on lymphocytes and antibodies. Both systems do not operate in isolation. In the afferent limb of the adaptive response, macrophages present the antigens in a genetically restricted interaction to lymphocytes, while at the effector level antibodies help phagocytes to recognize their targets. Additionally, a multitude of interleukins, secreted by lymphocytes and macrophages, regulate the bidirectional communication. The brain is an immunologically privileged region. Immune surveillance is accomplished by occasional patrol of T-cells, while phagocytosis is effected by resident microglia which are aided by blood-born macrophages.

Cumulating evidence indicates that the neuroendocrine and immune systems are intimately integrated into a holistic system that sustains a complex homeostatic network (Kemeny *et al*., 1992; Scapagnini, 1992; Mosley, 1996). Particularly, complex relationships operate between the HPA axis, the pituitary-thyroid axis, the pineal gland, respectively, and the immune system (Falaschi *et al*., 1994; Savastano *et al*., 1994; Fabris *et al*., 1995; Skwarlo-Sonta, 1996). Knowledge about the modulation of the immune system by, for example, NPY, M, NGF, DHEA, SS, and GH, is fragmentary (see part V of this series for further reading). Currently, only first insights into bidirectional relationships have been gained and the complex network is far from understood. Ageing compromises the delicate, finely tuned feed-forward and -backward communication loops (reviewed by Scapagini, 1992; Mosley, 1996; Mazzoccoli *et al*., 1997). Thymic involution is one of the processes secondary to neuroendocrine decline.

Immune senescence is characterized by both an immune deficiency and an immune dysregulated state (Burns and Goodwin, 1997; Grubeck-Loebenstein, 1997). In essence, the thymus-related specific cellular responses are impaired, while the basal unspecific humoral and cellular activity of the innate system is activated, although stimulated responses may be diminished. Ageing leads to a decline of T-cell counts and function. Memory cells increase, while naive T-cells decrease. This alteration of subsets is paralleled by an increase of anergic T-cells with reduced proliferative responses to antigen and mitogens. T helper type 1 (Th1) cytokines, interleukin (IL)-2 and interferon (IFN)-γ, are reduced, as is the expression of IL-2 receptors (Linton *et al*., 1997). Causally, the T-cell anergy appears to be related to an impaired signal transduction, a decreased cytosolic free Ca^{2+} concentration, diminished Ca^{2+} signal generation and increased Ca^{2+} extrusion (Miller, 1994; Rink and Seyfarth, 1997; Utsuyama *et al*., 1997). Likewise, natural killer cell function is impaired (Albright and Albright, 1998). Circulating B-lymphocytes are significantly decreased. B-cell function is also impaired, leading to an impaired response to foreign antigens and an increased production of autoantibodies and monoclonal immunoglobulins (Burns and Goodwin, 1997; Rink and Seyfarth, 1997). The dysregulation is characterized by a shift from adaptive antibody-mediated immunity with highly specific, high-affinity IgG antibodies reactive to foreign antigens to natural humoral immunity with low-affinity, polyreactive, IgM antibodies which react with autoantigens (Le Maoult *et al*., 1997). As shown in humans, mice and guinea pigs, granulocytes and monocytes/macrophages may exhibit functional deficits with ageing, characterized by a higher adherence and lower chemotaxis capacity, oxidative burst and phagocytosis (Mege *et al*., 1988; Forner *et al*., 1994; Albright and Albright, 1998). An increase in macrophage prostaglandin E2 production may contribute to the decreased T-cell function (Beharka *et al*., 1997). Proinflammatory cytokines secreted by activated macrophages such as IL-1, IL-3, IL-6, IL-8 and TNF-α are increased both in aged mice and humans (Paganelli *et al*., 1994; Rink and Seyfarth, 1997). These cytokines, together with likewise increased Th2 cytokines IL-4 and IL-10, also control B-cell differentiation and through isotype switch and Ig production they effect a significant increase in IgG subclasses and IgA, and IgM serum levels (Paganelli *et al*., 1994; Rink and Seyfarth, 1997). IL-1 stimulates the HPA axis in another endocrino-immunological feedback loop (Sapolsky *et al*., 1987; Rivier, 1994). Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons likewise indicate a chronic activation of the innate system (Ballou *et al*., 1996). Particularly, plasma IL-6 levels rise through life span, are elevated in healthy aged mice, rats, monkeys and humans (Ershler *et al*., 1993; Mysliwska *et al*., 1998) and are associated with functional disability in elderlies (Cohen *et al*., 1997; Mysliwska *et al*., 1998). Similarly, another marker of acute phase reactions, serum α_1-antichymotrypsin, was associated with cognitive impairment (Gabriel *et al*., 1998). However, while basal monocytic secretion rates seem to be elevated, their

functional reserve may be reduced. Activated aged human monocytes display a decreased cytotoxicity, reduced secretion of IL-1, IL-8, TNF-α, IFN-γ, stimulating factors and lower reactive oxygen release (McLachlan *et al*., 1995; Gon *et al*., 1996).

The brain also reflects these changes. Activated phagocytic microglia increase with ageing in the human, monkey and rat brain (DiPatre and Gelman, 1997; Sheng *et al*., 1998). The microglia may proliferate at a considerably accelerated rate (Morgan *et al*., 1995). However, phagocytic activity of these glial cells is decreased (Yu and McLaurin, 1998). Elements of the innate humoral immune response are upregulated. In association with the compromise of brain antioxidant defence, IL-1β levels are elevated (O'Donnell and Lynch, 1998). Basal production by glial cells of pro-inflammatory cytokines such as IL-6 is increased (Prechel *et al*., 1996; Yu and McLaurin, 1998) with potential adverse sequelae (Gruol and Nelson, 1997). Moreover, expression of lipoxygenase, which is a key enzyme in the synthesis of inflammatory eicosanoids, is upregulated in neurons of the aged brain, possibly contributing to the neuronal vulnerability (Uz *et al*., 1998). In humans, the CSF shows increased levels of complement components and membrane attack complex (Loeffler *et al*., 1997). A potential factor triggering these inflammatory changes may be AGE, which accumulate in the ageing brain. AGE complexing to AGE-binding proteins expressed by neurons and glial cells can upregulate granulocyte-macrophage colony stimulating factor (GM-CSF), which is able to induce proliferation and differentiation of myeloid precursors and could set in motion a cascade of inflammatory events (Li *et al*., 1998).

Ageing and the calcium–energy–redox triangle

The intricately interdependent calcium–energy–redox triangle regulates the vital cellular processes. While persistent procurement of energy, the motor of life, is the main purpose and evolutionary masterplan of this triangle, it is the master agent Ca^{2+} which keeps both energy homeostasis and generation of oxygen radicals under primary control. A perturbation of one of the variables may disrupt the delicate homeostasis with detrimental consequences for cellular function and integrity. In ageing, the triangle undergoes a progressive loss of fine-tuning. The causal relationships have been a matter of intense scientific discussion and various hypotheses have posited a causal role of mitochondrial dysfunction (Harman, 1972; Shigenaga *et al*., 1994), of oxidative stress (Harman, 1992), of Ca^{2+} dysregulation (Fujita, 1986; Disterhoft *et al*., 1994; Landfield, 1994) or a combination of all three (Ying, 1997b) in ageing. A multitude of modulators, e.g. hormones, establish a network of homeostatic control and regulation of the triangle. During the reproductive phase, the hormonal balance is well equipped for the maintenance of a trophic milieu. Post-reproductively, however, the resources of this trophic system dwindle gradually, exhausting the safety margin, deteriorating the functional reserves upon challenge and finally leading to an overt functional deficit. Since these processes are energetic in their last consequence, they are best demonstrable in the organ with the highest energy dependence, the CNS, but in principle they also apply for the other organs. By outlining these mechanisms, the basic features of a unifying concept of ageing have been presented. This concept will be extended and causal relationships will be outlined (Heininger, in preparation). Of importance in the context of this series, ageing lays the foundations for the manifestation of AD.

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