TREATMENT POSSIBILITIES OF ALZHEIMER'S DISEASE

I. Miklya[1, 2], P. Gaszner[3]
[1]Semmelweis University, Faculty of General Medicine, Department of Pharmacology and Pharmacotherapy, Budapest, Hungary
[2]Neuropsychopharmacological Research Unit of the Hungarian Academy of Sciences, Budapest, Hungary
[3]National Institute of Psychiatry and Neurology, Budapest

TERÁPIÁS LEHETŐSÉGEK ALZHEIMER-KÓRBAN

Az Alzheimer-kór ma is használatos gyógykezelése rövid összefoglalása (az anticholinerg, a glutamát neurotranszmisszió, a ß-amyloid teórián alapuló, az antioxidáns, a gyulladásgátlás hipotézise) világosan mutatja, hogy a hatás nem átütő erejű. Előrelépést jelent a Knoll-féle elképzelés, mely a mezenkefalon enhancer mechanizmusán alapuló anyagok, így a (-)-deprenyl és a (-)-BPAP- hatását írja le mind az Alzheimer-kórban, mind a Parkinson-betegségben. Nemzetközi statisztikai adatok utalnak arra, hogy 65 év felett a nők hétszer gyakrabban betegednek meg Alzheimer-kórban, mint a férfiak. A gyógykezelési lehetőségek felsorolásán túl a (-)-deprenyllel és (-)-BPAP-vel történő gyógyszerkipróbálás elméleti lehetőségét és gyakorlati útmutatását adja.

KULCSSZAVAK: Alzheimer-kór, ß-amyloid, (-)-deprenyl, (-)-BPAP, enhancer mechanizmus

SUMMARY

A brief summary of the current treatment of Alzheimer disease (AD) (cholinergic replacement therapy, influence of glutamatergic neurotransmission, treatment based on the -amyloid cascade theory, antioxidants, anti-inflammatory drugs) clearly proves that the applied strategies are practically inefficient. We describe therefore the rationale and design of a reasonable clinical trial to test the validity of Knoll's concept that the administration of a synthetic mesencephalic enhancer substance prior to the precipitation of the symptoms is our only chance to significantly reduce the prevalence of the two main neurodegenerative disorders AD and Parkinson's disease (PD). Considering that in the population over 65 there are substantial sex (68% female, 32% male) and geographical (highest rate: 10% in USA) differences in the incidence of AD, we propose to perform the clinical trial in 75-85 year old females in the USA. Individuals without (Group 1) and with (Group 2) predisposition to AD should be selected. One third in each group should be treated daily with placebo, (-)-deprenyl (1 mg) and (-)-BPAP (1 mg), respectively. Series of studies proved already the protective effect of the synthetic mesencephalic enhancer substances against age-related neurodegenerative changes in the brain. We may therefore expect a significant difference in the placebo versus drug treated groups in the number of individuals who will precipitate with the passing of time the symptoms of AD or PD. The introduction of a safe and efficient prophylactic therapy that significantly decreases the prevalence of AD is a necessity which cannot be further postponed.

KEYWORDS: Alzheimer´s disease, -amyloid, (-)-deprenyl, (-)-BPAP, enhancer mechanism

ABBREVIATIONS

Alzheimer's disease=AD
Parkinson's disease=PD
R-(-)-1-(benzofuran-2-yl)-2-propylaminopentane=(-)-BPAP
monoamine oxidase=MAO
Diagnostic and Statistical Manual of Mental Disorders, version IV, Text Revision=DSM-IV-TR

apolipoprotein-E4=APO-E4
amyloid precursor protein=APP
acetylcholinesterase=AChE
butyrilcholinesterase=BuChE
6-hydroxydopamine=6-OHDA
superoxide dismutase=SOD
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine=MPTP
1-methyl-4-phenyldpyridinium=MPP

INTRODUCTION

AD the age-related neurodegenerative disorder of unknown etiology that accounts for 65-70% of diagnosed dementia cases, is incurable. The disease affects by now about 15 million persons worldwide. As the number of individuals over 65 is estimated to soar to 1.1 billion by 2050 a sharp increase in the afflicted population is expected in the future. To find a measure to significantly decrease the prevalence of AD is now a pressing necessity that cannot be further postponed. A survey of the literature from this aspect, the evaluation of Knoll's concept that cherish the hope to reduce the prevalence of AD, and the proposal of a reasonable clinical trial to test the validity of this concept, is the aim of this review.

CURRENT STRATEGIES IN THE TREATMENT OF AD

Alois Alzheimer described in 1907 the form of dementia that bears his name. He was the first who pointed to a relationship between dementia and the extensive appearance of dense fiber-like tangles and darkly staining senile plaques in the cortical and hippocampal regions. The grave morphological changes lead to grave functional disturbances. For example, the loss of pyramidal neurons and their synapses necessarily lead to cholinergic and glutamatergic hypofunction. As the important role of these transmissions in cognitive and memory functions is well known, the current symptomatic treatment of AD is based on the correction of these hypofunctions.

As in AD reduction in acetylcholine synthesis, reduced cholin uptake, degeneration of cholinergic neurons, reduction in the density of muscarinic and nicotinic receptors were detected in the cortex and hippocampus, the conclusion was drawn that a cholinergic deficit plays a role in the cognitive, functional and behavioral symptoms of the disease. To reverse this deficit, acetylcholinesterase inhibitors (donepezil, galantamine, memantine, rivastigmine, tacrine) are administered. Long term clinical studies were already performed with donepezil (Winblad et al., 2001; Rogers et al., 2002).

Despite of the world-wide use of acetylcholinesterase inhibitors, there can be little doubt that with cholinergic replacement therapy no real improvement in AD can be achieved. Substantial adverse effects (nausea, diarrhoe, anorexia, etc.) accompany marginal therapeutic benefits. Muscarinic and nicotinic receptor agonists were found to be completely ineffective in AD (Lockhart and Lestage, 2003).

The neuronal loss in hippocampal and cortical regions in AD is necessarily leading also to a glutamatergic hypofunction. Glutamate, the excitatory amino acid, the transmitter of the cortical and hippocampal pyramidal neurons, plays a key role in cognitive functions and in the processes underlying learning and memory. Glutamate exerts its effects via ionotropic and metabotropic receptors. NMDA, AMPA and kainate receptors are the intensively studied ligand-gated ionotropic glutamatergic receptors (Fletcher and Lodge, 1996; Bleich et al., 2003; Francis, 2003).

Histologic studies proved the substantial loss of pyramidal neurons and their synapses in AD. The glutamate system is thought to play a role in neurological and psychiatric diseases due to an imbalance in glutamatergic neurotransmission. An overexcitation of the neurons may lead to death of nerve cells. It is suggested that an overactivation of NMDA-type glutamate receptors play a role in the pathogenesis of AD. This glutamate-mediated neurotoxicity is hoped to be antagonized by the administration of the uncompetitive NMDA antagonist, memantine (Danysz and Parsons, 2003). The neuroprotective effect of memantine (Jain, 2000) and the therapeutic effect of the compound in severely demented patients (Winblad and Poritis, 1999) was described. Nevertheless, the available data show no real promise to ever cure AD, or to prevent its development by influencing glutamatergic neurotransmission.

Another strategy to treat AD, the b-amyloid cascade theory, is based on post mortem verified neuropathological changes, the excessive appearence of which is claimed to be characteristic to the disease: accumulation of neurofibrillary tangles composed of hyperphosphorilated tau proteins and extracellular senile plaques containing b-amyloid1-40 and b-amyloid1-42 (Morishima, Kawashima and Ihara, 2002).

As b-amyloid1-42 is a neurotoxic agent. The hypothesis that this is a key molecule in the pathology of AD is now widely accepted (Selkoe, 2001), although the theory is controversial since the correlation between the concentrations and distribution of amyloid depositions in the brain and parameters of AD pathology, the degree of dementia, loss of synapses, loss of neurons, etc., is poor (Neve and Robakis, 1998).

As neurotoxicity is thought to be inseparable from oxidative injuries, free radicals, calcium and inflammatory-mediated processes, agents with

protective effect on cultured neurons, anti-oxidant compounds, and anti-inflammatory drugs are continuously tested in AD. As examples: vitamin E and selegiline (Sano et al. 1997; Grundman, 2000; Thomas, 2000; Kitani et al. 2002; Birks and Flicker, 2003), Ginkgo biloba extract (Ponto and Schultz, 2003), non-steroidal anti-inflammatory drugs (Etminan, 2003), estrogen (Schumacher et al., 2003) are administered.

Despite of the rapid growth of the number of papers that bears evidence of the seemingly frantic success of the b-amyloid cascade theory, the survey of the literature is furnishing unequivocal evidence that the therapy based on this strategy did not change the hopelessness of the patients who already developed AD. A radically new approach is needed to curb the predicted dramatic increase in the prevalence of AD.

Knoll's concept to reduce the prevalence of neurodegenerative disorders by the prophylactic administration of a synthetic mesencephalic enhancer substance

(-)-Deprenyl has been shown to slow the progression of PD (Tetrud and Langston 1989; Parkinson Study Group 1989) and AD (Sano et al, 1997), and is now a world-wide used drug, registered in 49 countries.

Interestingly, (-)-deprenyl is used now more and more out of its official approved use, as an anti-aging drug. It is believed to slow down general brain ageing, helping to prevent the onset of senile dementia, improve libido, enhance memory, and increase feeling of well-being. As also dozens of nootropics are claimed to exert such effects and are sold as true life extension compounds, a well-grounded suspicion accompanies the administration of any registered drug for a purpose out of its official approved use.

It seems right and proper that the majority of clinicians accept the so called anti-aging compounds with reserve. As a matter of fact, nobody described up to the present a brain mechanism of specified physiologic significance that is selectively influenced by any of the compounds classified as nootropics.

The case of the synthetic mesencephalic enhancer substances is, however, fundamentally different. From the very beginning (-)-deprenyl was described as a selectively acting MAO-B inhibitor (Knoll and Magyar, 1972, a paper which became in 1982 a Citation Classic), thus as a compound with not only a well-defined pharmacological effect, but also as a new entity which filled up a vac-uum in research. Later when it was realized that the compound is a PEA-derived synthetic mes-encephalic enhancer substance (Knoll et al. 1996), again an exactly defined specific effect of the drug was described that could be made clearly responsible for the therapeutic effect of (-)-deprenyl.

It is worth briefly run through the history of (-)-deprenyl that 40 years after its introduction is still in growing amounts world-wide administered, and being at present the only clinically avilable synthetic mesencephalic enhancer substance, cannot be substituted with any other registered drug.

The compound was introduced in 1965 as a new spectrum MAO inhibitor (Knoll et al., 1965). This was the time when MAO inhibitors fell into disrepute. In 1963, a calamitous number of clinical reports, demonstrating the occurrence of dangerous hypertensive attacks in patients treated with MAO inhibitors were published. Blackwell (1963) suggested that the hypertensive crises are associated with the ingestion of high amounts of tyramine, a releaser of noradrenaline from their stores in the nerve terminal, in cheese, the metabolism of which is inhibited by the MAO inhibitors (cheese effect). This conclusion was correct. Cheese and many other foods containing tyramine were found to be able to provoke hypertensive episodes in patients treated with MAO inhibitors. The cheese effect restricted the clinical use of this group of drugs.

Knoll found that in contrast to MAO inhibitors which potentiated the blood pressure effect of amphetamine, (-)-deprenyl did not potentiate, but inhibited the effect of amphetamine, another releaser of noradrenalin (see Fig. 1 in Knoll et al., 1965). It was exactly this peculiar effect of the compound that led to its selection for development (Knoll, 1983). Knoll et al. (1968) demonstrated in animal experiments that (-)-deprenyl is free of the cheese-effect and this was corroborated later in man (Elsworth et al., 1978; Sandler et al., 1978).

The real reason of the anomalic behavior of (-)-deprenyl was just recently clarified. PEA, the endogenous mesencephalic enhancer substance, is also a releaser of noradrenaline, and amphetamine shares this pharmacological spectrum with its parent compound. (-)-Deprenyl was the first synthetic PEA-derivative which lost the releasing effect of its parent compound but preserved its enhancer effect (see Knoll, 2001 for review).

In the same year when the unique behavior of (-)-deprenyl was published, Johnston (1968) described a substance, later named clorgyline, that

came into world-wide use as an experimental tool in MAO research. Johnston realized that clorgyline preferentially inhibits the deamination of serotonin. He proposed the existence of two forms of MAO, "type A" and "type B", being selectively inhibited by clorgyline and the latter relatively insensitive to it. Johnston's nomenclature has become widely accepted and is still in use.

For further studies a selective inhibitor of MAO-B was needed. It was shown in 1970 that (-)-deprenyl was the missing link, the highly selective inhibitor of MAO-B (Knoll and Magyar, 1972). The compound was used thereafter as the specific experimental tool to analyze MAO-B.

Knoll described in a series of papers the peculiar stimulatory effect of (-)-deprenyl on striatal dopaminergic activity (Knoll 1978, 1983). These results led him to formulate the first version of his concept that (-)-deprenyl, a selective inhibitor of MAO-B, should be given from age 45 as a prophylactic agent to slow the physiological age-related decline of the dopaminergic regulation in the brain (Knoll, 1982).

Let us quote the original justification of the hypothesis (Knoll, 1982, pp. 109-110):

"…well established old experiences offer a good explanation for the increase of brain MAO-B activity in the latter decades of life. Cell loss is a general feature of the aging brain. … As the loss of neurons is always compensated by glial cells, the progressive and cumulative loss of neurons in the aging brain gives a satisfactory explanation to the selective increase of extrasynaptosomal MAO-B activity with increasing age. This seems to be an unavoidable biochemical lesion of aging. … Collating the facts that there is an unavoidable loss of neurons, inescapably leading to increased MAO-B activity with increasing age, makes it understandable that dopaminergic and trace-aminergic modulation in the brain is progressively decreasing in the aging brain. It is in agreement with this trend of changes that an age-dependent decrease in the dopamine control of the basal ganglia in man was described, first by Bertler (1961), and corroborated by many others. Riederer and Wuketich (1976) found that the dopamine content of the human caudate nucleus decreased by 13% per decade over age 45.

If, in addition, we also consider that the activity of tyrosine hydroxylase, the enzyme catalysing the rate-limiting step in catecholamine biosynthesis, was also found to decrease in human brain tissue with increasing age (McGeer et al., 1971), weighty arguments seem to support the view that catecholaminergic tone is progressively decreasing in the aging brain.

As the described age-dependent chain of events can be deduced to well-defined biochemical lesions, the chances to develop a new drug strategy for counteracting or possibly even preventing, the adverse consequences of the age-related decrease of the catecholaminergic tone in the brain, are fair."

As can be followed in the series of consecutive reviews the results of the step by step published sets of experiments presented growing evidence in support of the hypothesis that (-)-deprenyl is a safe and efficient compound in slowing aging of the brain (Knoll, 1998, 2001, 2003).

Also in the light of our present knowledge there can be little doubt that because of the continuously increasing MAO-B activity in the aging brain, the more and more efficient metabolism of PEA works necessarily against the chances of a freshly synthetized PEA molecule to reach its target. As PEA is an endogenous mesencephalic enhancer substance, this is obviously one of the factors which contributes to the age-related decline of the mesencephalic enhancer regulation with the passing of time.

The same fits for dopamine. Knoll followed in longevity studies performed in male rats the age-related decline of a dopamine-dependent function, sexual activity (Knoll, 2001). Male CFY rats lose to the end of their 2nd year of life their ability to ejaculate. It was shown that the continuous administration of (-)-deprenyl shifted significantly the time of the disappearance of this function. In a study on 25-week-old male CFY rats, sexual activity (mounting, intromission, and ejaculation) was measured in four consecutive weekly mating tests. Altogether 90 rats, which displayed ejaculation in each of the four consecutive mating tests, were selected for the study. Thereafter half of the rats were treated with saline and half with (-)-deprenyl. Sexual activity was measured weekly until the animal lost completely the ability to ejaculate. The saline-treated rats lost this function within 112 ± 9 weeks, the (-)-deprenyl-treated ones within 150 ± 12 weeks (P<0.001) (Knoll, 1993).

In one of their longevity studies (Knoll et al., 1994) they selected from a large random population of young male rats (n=1600) the sexually inactive animals (low performing LP; n=94) and the sexually most active rats (high performing HP; n=99). They treated them with saline and (-)-deprenyl, respectively, until they died. HP rats, selected as the most active copulators, performed

significantly better on a learning test and lived significantly longer than their LP peers. For example, saline-treated LP rats lived 134.58±2.29 weeks, while their HP peers lived 151.24±1.36 weeks (p<0.001).

On the other hand, both LP and HP rats treated with (-)-deprenyl performed in fact significantly better in sexual and learning tests and lived longer than the saline-treated rats. For example, the lifetime of (-)-deprenyl-treated LP rats (152.54±1.36 weeks) was significantly (p<0.001) longer than the lifetime of their saline-treated peers (134.58± 2.29 weeks), and HP rats treated with (-)-deprenyl lived 185.30±1.96 weeks, significantly (p<0.001) longer than their saline-treated peers (151.24± 1.36).

The results of this study strongly supported the concept that the administration of a synthetic mesencephalic enhancer substance during the post-developmental phase of life is significantly slowing the age-related decline of the mesencephalic enhancer regulation.

Even convincing morphological evidence was presented in support of the concept that a synthetic mesencephalic enhancer substance slows aging of the neurocytes of the substantia nigra of rats. Tóth et al. (1992) developed a method, using TV-image analyzer, to compare different morphological parameters in the substantia nigra of young and old male rats. With the aid of this method, Knoll et al. (1992) determined the number, total area, area of one granule, and density features (sum and average of gray values and everage gray value of one pigment granule) of melanin granules in neurocytes of the substantia nigra in 3-month-old and 3-year-old male rats. The number of cells in sec-

tions of identical areas was similar in the young and old rats. A statistically non-significant difference between the two age cohorts in the proportion of neurocytes with and without melanin was found: 773 (48.1%) with and 853 (51.8%) without melanin in the young rats and 1219 (65.l%) with and 652 (34.8%) without melanin in the old ones. Within the melanin-containing neurocytes, however, statistically significant age-related differences in the number, area, and densitiy features of melanin granules were discovered. The majority of the neurocytes in young rats contained numerous, small-sized neuromelanin granules, whereas in the majority of the neurocytes of old rats, smaller numbers of large-sized neuromelanin granules were detected.

The mean number of neuromelanin granules in a neurocyte was 2600±1500 in 3-month-old rats and 1800±900 (p<0.001) in 3-year-old rats. The area of one granule was 49.000±18.800 μm2 in 3-month-old rats and 116.300±25.500 μm2 in 3-year-old rats. Thus, statisticaly significant age-related differences revealed by the TV-image analyzer allowed to check morphologically the influence of long-term (-)-deprenyl treatment on the neurocytes of the substantia nigra.

Table 1 shows results of the study in which the morphology of the neuromelanin granules was compared in the neurocytes of the substantia nigra of 3-month-old rats versus 21-month-old rats, treated with saline and (-)-deprenyl, respectively. The data clearly show that the lifelong treatment of the rats with (-)-deprenyl completely prevented the age-related morphological changes of the pigment granules in the neurocytes of the substantia nigra. This was unequivocal morphological evi-

Table I. Age-related changes in the number of neuromelanin granules and in the area of one granule in the neurocytes of the substantia nigra and prevention of these changes by (-)-deprenyl treatment (0.25 mg/kg, s.c. three times a week for 18 months). Data taken from Knoll, 1992, Table 4

NEUROCYTES FROM						
	3-month-old rats [young control-YC] (n=473)		21-month-old rats treated 18 months with saline [old control-OC] (n=481)		21-month-old rats treated 18 months with (-)-deprenyl[(-)-deprenyl-treated-DT] (n=503)	
	Mean	SD	Mean	SD	Mean	SD
(1) Number of neuro-melanin granules in a neurocyte	2,000	1,100	1,700	920	2,000	1,100
(2) Area of one granule (m^2)	39,600	25,000	75,000	30,600	39,800	19,600

(1) YC vs OC p<0.002; YC vs DT>0.05
(2) YC vs OC p<0.0001; YC vs DT>0.05

dence for the antiaging effect of prophylactic treatment with a synthetic mesencephalic enhancer substance.

The production of toxic free radicals is thought to play a leading role in the aging of neurons. The striatal system is perhaps the most endangered part of the brain as we lose 13% of our striatal dopamine in a decade after age 45. It is therefore an important argument in support of the antiaging effect of (-)-deprenyl that it protects the nigrostriatal neurons against different toxic effects (see Knoll, 2001 for review).

It was first shown by Knoll (1978) that (-)-deprenyl protects the striatum from the toxic effect of 6-OHDA. It was this finding that led to the assumption that (-)-deprenyl may enhance the scavanger function in the nigrostriatal dopaminergic neurons (Knoll, 1987). To find direct evidence, Knoll measured SOD activity in the rat striatum. This enzyme is known to play a key role in the detoxification of free radicals resulting from autooxidation of the endogenous metabolites of dopamine. He found that the daily administration of (-)-deprenyl for 3 weeks enhanced the activity of SOD in the striatum of both male and female CFY rats in proportion to the dose given (Knoll, 1988, 1989). (-)-Deprenyl has no direct effect on brain SOD activity in general. Using the cerebellum as a reference tissue, it was shown that the SOD activity in this area did not change in a statistically significant manner in (-)-deprenyl-treated male and female rats (Knoll, 1989). The (-)-deprenyl induced enhancement of the SOD activity in the striatum of rats was found to be unrelated to the MAO inhibitory effect of the drug. Clorgyline, one of the most potent MAO inhibitors, inhibited rather than enhanced striatal SOD activity in rats (Knoll, 1988, 1990).

The finding that (-)-deprenyl treatment increases SOD activity in the striatum of rats was first confirmed by Carrillo et al. (1991). They found a significant increase in catalase activity as well. Carrillo et al. also corroborated the finding that (-)-deprenyl enhances scavanger function in the striatum selectively. No significant change in the SOD and catalase activity could be detected in the hippocampus, which they used as a reference tissue (Carrillo et al. 1992). The effect of (-)-deprenyl on the anti-oxidant enzymes in brain was studied thereafter in detail (see Kitani et al. 2002 for review).

A series of studies proved that (-)-deprenyl protects neurons against a couple of neurotoxic agents. As discussed above (-)-deprenyl protected the nigrostriatal dopaminergic neurons against the toxic effect of 6-OHDA (Knoll, 1978). This was the first experimental evidence that (-)-deprenyl protects neurons against the effect of a selective neurotoxin. It was shown later that (-)-deprenyl, protects monkeys from the effect of the highly selective striatal neurotoxin, MPTP (Cohen et al., 1984), exerts a protection also against MPP^+ (Vizuete et al., 1993, Wu et al., 1993), and against the noradrenergic neurotoxin, DSP-4 (Finnegan et al., 1990).

During the last decade there was a rapid increase in the number of publications analyzing the neuroprotective, antiapoptotic, even antitumor effect of (-)-deprenyl under different experimental conditions (Knoll, 2001; Ebadi et al., 2002; Maruyama et al., 2002; ThyagaRajan and Felten, 2002; Tatton et al., 2003).

The discovery of the mesencephalic enhancer regulation and the realization that not only PEA but also tryptamine is an endogenous mesencephalic enhancer substance (Knoll, 1994), led to the development of (-)-BPAP, the tryptamine-derived enhancer substance that is highly selective and at least hundred times more potent than (-)-deprenyl in enhancing the activity of the catecholaminergic and serotonergic neurons in the mesencephalon (Knoll et al. 1999).

(-)-BPAP is the presently known most potent synthetic mesencephalic enhancer substance. (-)-BPAP significantly enhanced in 0.18 nM concentration the impulse propagation mediated release of ^{3}H-noradrenaline and ^{3}H-dopamine and in 36 picoM concentration the release of ^{3}H-serotonin from the isolated brain stem of rats. The amount of catecholamines and serotonin released from isolated discrete rat brain regions (dopamine from the striatum, substantia nigra and tuberculum olfactorium, noradrenaline from the locus coeruleus and serotonin from the raphe) enhanced significantly in the presence of 10^{-12}–10^{-14} M (-)-BPAP. This compound protected cultured hippocampal neurons from the neurotoxic effect of -amyloid$_{25-35}$ in 10^{-14} M concentration. In rats (-)-BPAP significantly enhanced the activity of the catecholaminergic and serotoninergic neurons in the brain 30 mins after acute injection of 0.1 g/kg s.c. In the shuttle box, (-)-BPAP was in rats about 130 times more potent than (-)-deprenyl in antagonizing tetrabenazine-induced inhibition of performance. This new enhancer substance seems to be a great promise for the future.

Knoll presented convincing experimental evidence which proved that the enhancer effect of

(-)-deprenyl is fully responsible for the beneficial therapeutic effect of this synthetic mesencephalic enhancer substance (Knoll, 1998). The present formulation of the concept (Knoll, 2001) that prophylactic (-)-deprenyl treatment should start immediately after sexual maturity was reached, deserve serious consideration. It was shown namely that mesencephalic enhancer regulation in the rat brain starts working on a significantly higher activity level at the end of the 3rd week of age, that is the discontinuation of breast feeding, the crucially important first step to live separately from the mother (Knoll and Miklya, 1995).

Weaning is obviously the onset of the developmental ("uphill") phase of the individual life of the mammalian organism (Knoll, 1994, 2001). The period, characterized by a higher basic activity, lasts until the rat develops full scale sexual maturity. One of the telltale signs which makes the operation of the mesencephalic enhancer mechanism evident is the enhanced basic activity of the catecholaminergic and serotonergic systems, as measured by the significantly enhanced release of catecholamines and serotonin from discrete brain regions isolated from the brain of rats after weaning. As sexual maturity was reached, this change disappeared and the basic activity of the catecholaminergic and serotoninergic systems returned to the preweaning level (Knoll and Miklya, 1995).

Sexual hormones seem to be responsible for the transition from the developmental, uphill phase of life, into the postdevelopmental, downhill period, characterized by the slow age-related decay of brain performance terminated by natural death (Knoll et al., 2000). Weighty arguments speak in favour for the assumption that the slow, continuous age-related decline of the enhancer regulation in the mesencephalic neurons plays a key role in the irresistible decay of behavioral performances with the passing of time.

All in all, there can be little doubt that in the downhill period of life there is an irresistible, physiologic decrease in the quality of life due to the continuous decline of the mesencephalic enhancer regulation. In the light of the peculiar age-related changes, the concept, first proposed in 1982, to slow brain aging by the lifelong prophylactic medication with a small dose of a safe, specific, potent synthetic mesencephalic enhancer substance, starting at the transition from the uphill to the downhill period of life (Knoll, 1982), seems reasonable.

This concept was substantially supported by the longevity study performed with (-)-deprenyl be-tween 1984 and 1988 showing that this drug prolongs life (Knoll, 1988). The finding was soon corroborated (Milgram et al., 1990; Kitani et al., 1992). Thereafter a growing number of experimental and clinical studies showed that (-)-deprenyl acts as a unique antiaging drug in both animals and humans. Prophylactic (-)-deprenyl medication slows the physiologic age-related decay of the catecholaminergic neurons in the mesencephalon, thereby slowing the decay of behavioral performances with the passing of time and prolongs life (Knoll, 1998, 2001).

The physiological aging of the brain, from which there is no escape, is a continuum. If an individual lives long enough, normal ageing leads over 65 unavoidably to age-associated memory and cognitive decline, but because of the extreme individual differences in the capacities of learning and memory storage, the rate of decay can only be estimated by the exact knowledge of the original behavioral performances of the person. The post mortem verified neuropathological changes in the brain in AD, loss of neurons in the cortex and hippocampus, accumulation of neurofibrillary tangles and extracellular senile plaques containing -amyloid, differ only quantitatively from changes detectable in the normally ageing human brain. According to Knoll's concept, the age-related progressive, physiological decay in brain performances rests primarily on the decay of the mesencephalic enhancer regulation that works as the engine of the brain (Knoll, 2003). He pointed already in the first version of his concept to the dramatic age-related decrease of the striatal dopamine content in the human brain (Knoll, 1982). We lose 13% of our striatal dopamine in a decade after age 45! Thus, the efficiency of the mesencephalic catecholaminergic machinery is progressively decreasing with the passing of time. As the brain engine keeps the cortical neurons active in drive motivated, goal-seeking behavior, this means that parallel with the mesencephalic enhancer regulation also cortical activity is on a progressive, age-related functional decline.

On the other hand, Knoll points to the fact that humans possess a practically immense cortical capacity. They are born with hundreds of billions of cortical neurons of which a negligible part only can change functionally through learning during human life time. It seems therefore unreasonable to relate the age-associated decline in the learning capacity and memory storage to a loss of cortical neurons. The more so, since in contrast to earlier belief, the age-associated loss of cortical neurons

is not substantial and even its highest rate in AD is too modest to explain the memory and cognition decline in the aging brain (Peters et al. 1994).

It is the essence of Knoll's concept that the overwhelming majority of the human population dies before the age-related decay in the mesencephalic enhancer regulation, and as a consequence of it in the cortical neuronal function, exceeds the critical threshold beyond of which the characteristic symptoms of PD and AD, respectively, are precipitated. As neurodegenerative disorders seem to root in premature rapid aging of specific groups of neurons in the brain for unknown origin, it is the logic that the administration of a small daily dose of a synthetic mesencephalic enhancer substance from sexual maturity until death which slows significantly the age-related decline of the mesencephalic enhancer regulation may significantly decrease the prevalence of PD and AD.

Outlines of a clinical trial for testing the potential of synthetic mesencephalic enhancer substances, (-)-deprenyl, (-)-BPAP, to decrease the prevalence of AD

According to Knoll the mesencephalic brain engine keeps in the developmental phase of life and in the early phase of postdevelopmental longevity the telencephalic neurons continuously active. These neurons fight successfully against their self-produced harmful metabolites. Due to the irresistible slow decay of the mesencephalic enhancer regulation as a function of age, the beneficial influence of the brain engine on the telencephalic neurons is on a progressive decline. As a result of this process, with the passing of time, even morphologically traceable age-related neurodegenerative changes appear in the highly sensitive, most sophisticated telencephalic neurons.

AD, an irreversible loss of neurons primarily in the cortex and hippocampus leading to progressive impairment in memory, judgement, decision making, etc., is the worst outward form of brain aging. An analysis of the prevalence of AD as a function of age makes it clear that this is just a grave form of the natural aging of the human brain.

The mean age at the onset of AD is approximately 80 years, and the manifestation of the illness before the age of 60-65 years is very rare. In the age cohort 65-69 AD has a prevalence of 1% only. This increases to about 20% in the 85-89 year old group and the risk to precipitate the disease can reach the 50% level among persons 95 year of age

and over (Campion et al., 1999; Hy et al., 2000; Helmer et al., 2001; Nussbaum and Ellis, 2003).

There are special genetic risk factors for AD, like e.g. the 4 allele of the apolipoprotein-E (APOE) gene , isotonic variation in CYP46, CYP46*C, that significantly increase the risk of AD development (Bookheimer et al., 2000; Borroni et al., 2003). Although it seems reasonable to assume that the majority of those who precipitate the disease are carriers of risk factors, it is hard to see how this knowledge can ever help us to fight off the disease.

Collating all the facts we know at present about AD its seems to us that from therapeutic point of view the logic step forward in our effort to fight of AD is to check the validity of Knoll's concept, and find out the effectiveness of the selective enhancement of the activity of the brain engine, the effort to keep as long as possible the cortical and hippocampal neurons on a higher activity level by the aid of the administration of a syntetic mesencephalic enhancer substance.

In the population over 65 there are substantial sex (68% female, 32% male) and geographical (highest rate: 10% in the USA) differences in the incidence rate of AD (see Lockhart and Lestage, 2003 for review).

We therefore propose to perform the clinical trial in 75-80 year old females in the USA who did not show in a proper series of tests any sign of dementia. The candidates for the trial should be selected according to their predisposition to AD. Group 1: carriers of the APOE 3 allele (individuals without predisposition to AD), and Group 2: carriers of the APOE 4 allele (individuals with predisposition to AD). One third in each group should be treated with placebo, (-)-deprenyl and (-)-BPAP (1 mg/day), respectively. In case of 1000 participants in each group, and with the expectation that 5% will precipitate the symptomes of AD within 5 years, this would allow to answer the following questions:

(1) are synthetic mesencephalic enhancer substances capable to significantly decrease the incidence rate of AD?

(2) is the incidence rate for the precipitation of AD higher in carriers of the APOE 4 allele than in carriers of the APOE 3 allele?

(3) is (-)-BPAP more effective than (-)-deprenyl?

Correspondance:
Dr. Peter Gaszner
1021 Budapest, Hűvösvölgyi út. 116.

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