Molecular Psychiatry (2016) 21, 1499–1503

www.nature.com/mp

REVIEW

The significance of selegiline/(−)-deprenyl after 50 years in research and therapy (1965–2015)

I Miklya

Deprenyl/Selegiline (DEP), created by Joseph Knoll in the 1960s, registered in more than 60 countries to treat Parkinson's disease, Alzheimer's disease, major depressive disorder; and used as an anti-aging drug, achieved its place in research and therapy as the first selective inhibitor of B-type monoamine oxidase (MAO-B). The demonstration that the DEP analog (−)-1-phenyl-2-propylaminopentane devoid of MAO inhibitory property, enhanced like DEP the activity of the catecholaminergic brain engine revealed that this effect is unrelated to the selective inhibition of MAO-B. β-Phenylethylamine (PEA), the important trace-amine in the mammalian brain, is known to be a releaser of catecholamines. Amphetamine and methamphetamine, the best known synthetic PEA derivatives are also releasers of catecholamines like their parent compound. DEP is a unique synthetic PEA derivative devoid of the catecholamine releasing property. As the releasing effect conceals the catecholaminergic activity enhancer (CAE) effect, it remained undiscovered until DEP uncovered that PEA is a natural CAE substance; and only releases catecholamines in high concentration. Discovering that tryptamine is a natural enhancer of catecholaminergic and serotonergic neurons catalyzed the development of R-(−)-1-(benzofuran-2-yl)-2-propylaminopentane (BPAP); the most potent and selective enhancer substance, and it exerts its enhancer effect in 0.0001 mg kg^{-1}. DEP and BPAP initiated an analysis of the enhancer regulation in the mammalian brain. Studies regarding the nature of the enhancer regulation revealed that this regulation is enhanced after weaning and sex hormones return it to the pre-weaning level. Thus, sex hormones elicit the transition of the developmental phase of life into the post-developmental, downhill (aging) period. The aging-related, slow decline in the enhancer regulation of the catecholaminergic brain engine, the main activator of the cortex, is the prime factor of brain aging. The enhancer regulation's decay in the most rapidly aging dopaminergic system is, for example, mainly responsible for the decline in learning ability and sexual activity over time. According to the Knoll concept, based on two longevity studies performed on male rats, to keep the catecholaminergic brain engine, from the beginning of the downhill period of life, via the administration of a small daily dose of a CAE substance (presently DEP is the only available drug) on a higher activity level, thus to fight against the physiological aging-related slow decay of the catecholaminergic system, is a suitable anti-aging therapy. As our present knowledge regarding the enhancer regulation in the mammalian brain is like seeing a peak of an iceberg, the future of this new line of brain research looks promising from both theoretical and practical aspects.

Molecular Psychiatry (2016) **21,** 1499–1503; doi:10.1038/mp.2016.127; published online 2 August 2016

DEVELOPMENT OF DEPRENYL

Knoll started in the early 1950s behavioral studies on rats and realized the extraordinary importance of the catecholaminergic brain machinery (the engine of the brain) in the fixation of acquired drives. To stimulate the brain engine he used amphetamines, releasers of catecholamines, which unforeseeably disturb purposeful behavior. To avoid this side effect he designed and performed a structure–activity relationship study and selected E-250, later named deprenyl, for detailed analysis. The first publication in English appeared in 1965 and the (−)-enantiomer, (R)-N-methyl-N-(1-phenylpropan-2-yl)-prop-1-yn-3-amine [Selegiline, (−)-Deprenyl (DEP)] was developed.[1]

THE UNIQUE MAOI DEVOID OF THE 'CHEESE EFFECT'

Knoll designed E-250 as a new antidepressant. Both (±)-E-250[2] and (−)-E-250[3] (DEP) were shown by Varga to be prompt acting antidepressants. The finding was first confirmed by Mann and Gershon[4] and later in numerous papers. In 2002 Bodkin and Amsterdam published their first clinical trial with a new DEP preparation, the selegiline-transdermal system (STS).[5] In 2006 the FDA approved STS (Emsam) for depression.

THE FIRST SELECTIVE INHIBITOR OF MAO-B

In 1963, in *Lancet*, a calamitous number of clinical reports gave accounts of patients treated with monoamine oxidase inhibitors (MAOIs) that temporarily developed hypertensive crises. Blackwell suggested that the symptoms are associated with the ingestion of high amounts of tyramine in cheese, the metabolism of which is inhibited by the MAOIs ('cheese effect').[6] This side effect restricted their clinical use. Knoll's discovery that DEP is a unique MAOI free of the 'cheese effect';[7] and this was verified in 1978 in human studies;[8,9] was of notable therapeutic importance. DEP's safety made it possible to combine levodopa+DEP in Parkinson's disease (PD).[10]

Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary. Correspondence: Dr I Miklya, Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest 1089, Hungary.
E-mail: miklya.ildiko@med.semmelweis-univ.hu
Received 2 July 2015; revised 30 November 2015; accepted 15 December 2015; published online 2 August 2016

Knoll presented in 1971 at the First International MAO Symposium that DEP is a selective inhibitor of B-type MAO (MAO-B).[11] The paper has become a citation classic, and DEP is still a key important experimental tool in MAO research.

FIRST CLINICAL TRIAL OF DEP IN PD

Because of the serious side effects of levodopa in PD, Birkmayer and Hornykiewicz attempted to achieve a levodopa-sparing effect with the concurrent administration of levodopa with an MAO inhibitor, but the frequently elicited hypertensive attacks terminated this trial.[12] Birkmayer combined first DEP with levodopa and achieved a levodopa-sparing effect without signs of hypertensive reactions.[10] This study and a *Lancet Editorial* (25 September 1982) initiated the world-wide use of DEP in PD.

FIRST PROOF OF THE NEUROPROTECTIVE EFFECT OF DEP

It was first shown by Knoll and his coworkers[13] in the late 1970s that DEP treatment protects the dopaminergic neurons from the toxic effect of the specific dopaminergic neurotoxin, 6-hydroxydopamine (6-OHDA). DEP protects the striatum from the toxic effects of 6-OHDA via the blockade of B-type MAO, the inhibition of 6-OHDA uptake into the neuron, the facilitation of scavenger function, and improved removal of neurotoxic free radicals.[14] These conclusions catalyzed the discovery that DEP is significantly enhancing the activity of superoxide dismutase in the striatum.[15]

Further studies revealed that DEP protects neurons against a variety of neurotoxic agents: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DSP-4; 5,6-dihyroxyserotonin; AF64A; increases production of neurotrophins (nerve growth factor, brain-derived neurotrophic factor and glial cell-derived neurotrophic factor) which are natural protective agents of neurons; has an immunostimulant effect; increases interleukin (IL-2) and natural killer cell activity; inhibits tumor growth, serum prolactin and suppresses brain monoamine metabolism in rats with carcinogen-induced mammary tumors; and is associated with enhanced central and peripheral neurotransmission and immune activity.

CONCEPTUAL DEVELOPMENT THAT MAINTENANCE ON DEP IMPROVES THE QUALITY OF LIFE IN THE LATTER DECADES

In 1981, Knoll defined his hypothesis that a progressively developing catecholaminergic and trace-aminergic deficiency is responsible for the biochemical lesion in the aging brain which leads to the age-related decline in sexual and learning performances and ultimately natural death,[16] and soon proved that this effect of DEP is unrelated to the inhibition of MAO-B.[17]

We lose 13% of our brain dopamine in the decade after age 45.[18] It is well established that during post-developmental longevity there is also a continuously increasing PEA deficit in the mammalian brain. As a rule, enzyme functions decrease in the brain with the passing of time. MAO-B is an exception; its activity is progressively increasing in the aging human brain.[19] Also, the activity of tyrosine hydroxylase, the enzyme catalyzing the rate-limiting step in catecholamine biosynthesis, decreased in human brain tissue with increasing age.[20]

FIRST TRIAL TO TEST THE REALITY OF HIS CONCEPT

Knoll proposed to Birkmayer, at that time the only clinician who treated hundreds of his patients with Madopar+DEP, to analyze the influence of DEP treatment on the survival of his patients. In an open, uncontrolled study, the long term (9 years) effect of treatment with Madopar alone ($n = 377$) or in combination with DEP ($n = 564$) was compared in parkinsonian patients. The survival analysis revealed a significant increase in the life expectancy of the Madopar+DEP group regardless of the demographic differences between the groups.[21]

FIRST LONGEVITY STUDY WITH DEP

The study was performed on 2-year old, long living, robust, Wistar–Logan male rats. Rats were treated three times a week subcutaneously with saline (0.1 ml per 100 g) and DEP (0.25 mg kg^{-1}), respectively, until they died. As a measure of striatal function, sexual activity was tested once a week in a group of rats ($n = 132$) from the 24th month of their life. Due to aging-related decay, none of the 2-year-old animals displayed full scale sexual activity (mounting, intromission and ejaculation).

DEP treatment restored full scale sexual activity in 64 out of 66 rats. The first longevity study with DEP furnished unequivocal experimental evidence that prophylactic DEP treatment significantly prolongs the life of rats.[15,22]

The discovery that DEP treatment is significantly enhancing scavenger function in the striatum of rats,[15] but leaves superoxide dismutase activity in the cerebellum unchanged[23] signals the specific CAE effect of DEP. This finding was corroborated in 1991 (ref. 24) and studied later in detail.

Knoll outlined the hypothesis that, as the activity of the catecholaminergic system can be improved at any time during life, it must essentially be feasible to develop a technique for transforming a lower-performing, shorter-living individual, to a better-performing, longer-living one. It, therefore, demonstrates that a shift in the duration of life beyond the technical life span, with a yet unpredictable upper limit, must be possible in all mammals, including the human race.[25]

SECOND LONGEVITY STUDY WITH DEP

The aim of this study was to test how DEP treatment transforms a lower-performing, shorter-living rat to a better-performing, longer-living one. Out of 1600 sexually experienced male rats, the 94 sexually inactive (low performing) and the 99 most sexually active (high performing, HP) rats were selected. The rats were treated from the eigth month of life three times a week, subcutaneously, with saline (0.1 ml per 100 g) and DEP (0.25 mg kg^{-1}), respectively, until they died. Their copulatory activity was tested once a week, and their learning performance was measured in the shuttle box once every three months.

The saline-treated low-performing rats never displayed ejaculation during their lifetime, and they were extremely low performers in the shuttle box. Their DEP-treated peers became sexually active. Their mating performance was substantially increased and lived significantly longer than their salt-treated peers and as long of time as the salt-treated HP rats. The salt-treated HP rats were sexually active, and their learning performance was high. The DEP-treated HP rats were much more sexually active than their salt-treated peers. Also, their learning performance substantially increased. They lived significantly longer than their salt-treated peers. Out of 50 rats, 17 lived longer than the maximum life span observed in the strain used in the study.[26]

The finding that DEP treatment prolongs life was confirmed by rats; mice; Syrian hamsters; beagle dogs; and even *Drosophila melanogaster*.

PROOF THAT DEP TREATMENT DELAYED THE NEED FOR LEVODOPA THERAPY

Tetrud and Langston[27] published first that a double-blind, placebo-controlled study on 54 patients with early PD, randomly assigned to DEP (10 mg per day) or placebo treatment groups and followed until levodopa therapy was indicated, showed that the average time until levodopa was needed was 312.1 days for

patients in the placebo group and 548.9 days for patients in the DEP group.

The DATATOP multicenter clinical trial that spanned 23 Universities in the USA and Canada, studied the ability of DEP and α-tocopherol, antioxidant agents that act through complementary mechanisms. Eight hundred patients were randomly assigned to a two-by-two factorial design to receive DEP, α-tocopherol, a combination of both drugs, or placebo, and were followed up to determine the frequency of development to the end point. Due to the continuous deterioration of the nigrostriatal dopaminergic neurons in PD, usually within one year after diagnosis of the disease, patients need dopamine substitution (levodopa therapy). DEP treatment significantly delayed the need for levodopa. By the end of the trial, 57% of patients who received DEP did not need levodopa treatment, and these patients also had a significant reduction in having to give up full time employment. In contrast, α-tocopherol was ineffective.[28]

French, Swedish and Norwegian-Danish multicenter studies confirmed this unique beneficial effect of DEP treatment in *de novo* PD.

Since the mid-1980s, more and more convincing experimental data indicated that the enhancement in the activity of the catecholaminergic brain engine with DEP treatment is unrelated to the selective inhibition of B-type MAO.[29,30,31] The ineffectiveness of α-tocopherol in the DATATOP study was in harmony with this approach, which was later validated: DEP is enhancing the impulse propagation-mediated release of dopamine (catecholaminergic activity enhancer (CAE) effect), α-tocopherol is devoid of this property,[32] proving that the CAE effect was responsible for the effectiveness of DEP in the DATATOP study.[33] The clinical trial performed by the Parkinson Study Group with rasagiline, a selective inhibitor of MAO-B, revealed that unlike the early selegiline trials, rasagiline, also devoid of the CAE effect,[34] did not decrease the need for levodopa.[35]

DEVELOPMENT OF (−)-1-PHENYL-2-PROPYLAMINOPENTANE

Knoll developed (−)-1-phenyl-2-propylaminopentane, a DEP analog, which is as equally active with DEP in enhancing the activity of the catecholaminergic brain engine, but it is devoid of MAOI property. This study furnished primary evidence that the main effect of DEP, the specific stimulation of the catecholaminergic brain engine, is unrelated to MAO inhibition.[31]

EVIDENCE THAT DEP TREATMENT PREVENTS AGING-RELATED PIGMENT CHANGES IN THE SUBSTANTIA NIGRA OF RATS

As neuromelanin is a marker of aging, Knoll and his coworkers developed a procedure for measuring the number, total area, area of one granule and density features of melanin granules in neural cells of the substantia nigra in groups of 3-month-old and 3 years old male rats. The majority of the neural cells in young rats contained numerous, small-sized neuromelanin granules, whereas in the majority of neural cells of old rats, a smaller number of large-sized granules were detected. DEP treatment completely prevented aging-related pigment changes.[36]

EVIDENCE THAT MULTIPLE, SMALL DOSE ADMINISTRATION OF DEP, WHICH LEAVES MAO-B ACTIVITY UNCHANGED, KEEPS CATECHOLAMINERGIC NEURONS ON A SIGNIFICANTLY HIGHER ACTIVITY LEVEL

Rats of both sexes were injected subcutaneously, daily for 21 days, with 0.1 ml per 100 g saline or with one of the following doses of DEP: 0.01, 0.025, 0.1 and 0.25 mg kg^{-1}. On brain samples removed 24 h after the last injection, the amount of biogenic amines released from the tissue within 20 min was measured: dopamine from the striatum, substantia nigra and tuberculum olfactorium; norepinephrine from the locus coeruleus; and serotonin from the raphe. Compared with the saline-treated rats, 3-week daily treatment even with the lowest dose of DEP (0.01 mg kg^{-1}) kept the catecholaminergic neurons working on a significantly higher activity level.[37] These experiments revealed to Knoll the existence of a key important mechanism, the enhancer regulation, in the mammalian brain. A new period of DEP research began with this concept.

CHARACTERISTIC CHANGES IN THE ENHANCER REGULATION OF THE CATECHOLAMINERGIC AND SEROTONERGIC NEURONS IN THE DEVELOPMENTAL VERSUS POST-DEVELOPMENTAL PHASES OF LIFE

In the rat, the interval from weaning (third week of life) until the end of the second month of age is the decisive developmental period; the animal acquires crucial abilities for survival and maintenance of the species. On the basis of the observation that 2-month-old starved rats are significantly more active than their 4-month-old peers, Knoll's lab checked their dopaminergic, noradrenergic and serotonergic activities in the brain before weaning (in 2-week-old rats), during the crucial developmental phase, from weaning to sexual maturity (in 4- and 8-week-old rats) and in the early post-developmental phase of life (in 16- and 32-week-old rats). As an indicator of the basic activity of catecholaminergic and serotonergic neurons in the brain, Knoll and his coworkers measured the amount of dopamine released from the striatum, substantia nigra and tuberculum olfactorium; norepinephrine from the locus coeruleus; and serotonin from the raphe.

From weaning until the end of the second month of life the striatal dopaminergic system of rats was significantly more active than either before or after that period. There was a marked increase in the amount of dopamine released from the striatum and tuberculum olfactorium after weaning (4th week), and its return to the pre-weaning level (2nd week) in sexually mature rats (32nd week). The amount of norepinephrine released from the locus coeruleus and the release of serotonin from the raphe in the resting state showed the same dramatic increase after weaning, and return to the pre-weaning level in sexually mature rats.[38]

These findings indicate that safe and effective measures are needed to maintain the catecholaminergic brain engine at a higher activity level during the aging period of life.

DEMONSTRATION THAT PEA IS A MIXED ACTING SYMPATHOMIMETIC

Because of the effects of PEA, it was and has remained common knowledge that the trace-amine is an indirectly acting sympathomimetic agent which acts via displacement of catecholaminergic transmitters from their storage sites. The discovery of the enhancer regulation in the mammalian brain revealed that PEA, the physiologically important trace-amine in the mammalian brain known as a classic releaser of catecholamines from their intraneuronal pools, is primarily, in low concentrations, a natural CAE substance, a selective enhancer of the impulse propagation-mediated release of catecholamines; and only in high concentrations a releaser of catecholamines.[39]

Amphetamines, the PEA derivatives not metabolized by MAO, are like PEA, their parent compound, CAE substances, and in higher concentrations, releasers of catecholamines. The releasing effect of PEA, and amphetamines concealed their CAE effect. It was the development of DEP, the first PEA derivative devoid of the catecholamine releasing property which rendered possible the discovery of the CAE effect of PEA and amphetamines.[40]

DEP IN THE TREATMENT OF AD

The first two studies demonstrating the beneficial effect of DEP in AD were published in 1987.[41,42] A series of clinical studies with small sample sizes confirmed the usefulness of this drug in the treatment of the disease.

The rationale and design of the first multicenter study of DEP in the treatment of AD using novel clinical outcomes were published in 1997.[43] The study concluded that in patients with moderately severe impairment from AD, treatment with DEP slows the progression of the disease.

DEP's value in the treatment of AD was the subject of a meta-analysis. There was a statistically significant difference at 4–6 weeks for daily activities, which later disappeared at assessments at 8–17 weeks.[44]

Beneficial effects of DEP treatment on cognitive dysfunctions of aged pet dogs and cats are in harmony with clinical experiences with AD. DEP (Anipryl) was the first agent approved for cognitive dysfunction syndrome therapy in dogs.[45] Up to now, the largest amount of research on dogs is conducted with DEP studies.

DEVELOPMENT OF BPAP

The discovery that tryptamine is like PEA, a natural enhancer substance,[25] initiated the development of BPAP, a much more potent enhancer than DEP, which is enhancing the activity of the catecholaminergic and serotonergic neurons in femto-picomolar concentrations.[46] DEP is basically ineffective on the serotonergic system.

It was shown in 2002 that a bi-modal, bell-shaped concentration effect curve is characteristic in the enhancer effect.[47] For example: Tetrabenazine treatment inhibits the acquisition of a conditioned avoidance response in rats in the shuttle box. Due to its enhancer effect, DEP is antagonizing the effect of tetrabenazine in the low-dose range, with a peak at 0.001 mg kg^{-1} ('specific enhancer effect'), and in the high-dose range with a peak of 0.25 mg kg^{-1} ('non-specific enhancer effect'), which blocks also MAO-B activity in the brain.[40] This shows that in both research and therapy, 0.25 mg kg^{-1} DEP has two effects: it selectively blocks MAO-B activity and exerts its non-specific enhancer effect.

Although there is good reason to believe that the enhancer effect of DEP is responsible for the observed changes, only experiments with BPAP could clarify the role of the enhancer effect of DEP in the recited data. BPAP is much more potent than DEP in antagonizing the tetrabenazine-induced learning deficit in the shuttle box: 0.0001 mg kg^{-1} is the peak dose with the specific enhancer effect, and 0.05 mg kg^{-1} is the peak dose with the non-specific enhancer effect.[40]

SEX HORMONES (ESTRONE AND TESTOSTERONE) TERMINATE THE SIGNIFICANTLY ENHANCED ACTIVITY OF THE CATECHOLAMINERGIC AND SEROTONERGIC NEURONS IN THE BRAIN, CHARACTERISTIC TO THE POST-WEANING PERIOD

As rats have a significantly more pronounced enhancer regulation working in the catecholaminergic and serotonergic neurons from the discontinuation of breast feeding until the appearance of sexual hormones, the increased enhancer regulation between weaning and sexual maturity is obviously responsible for the exuberant physical strength and mental vigor in the uphill period of life. It is reasonable that sex hormones have a key role in terminating the developmental phase of life. The regulation of sex hormones starts working in rats with full capacity only at the end of their 2nd month of age. This rapid decrease in catecholamines and serotonin from selected discrete brain regions appeared synchronously with the completion of sexual maturity. A careful analysis revealed that estrone and testosterone, but not progesterone dampens the enhancer regulation in the catecholaminergic and serotonergic brain stem neurons, and this is the mechanism which terminates developmental longevity as well.[48]

According to the Knoll concept, to keep the catecholaminergic brain engine, from the beginning of the downhill period of life, via the administration of a small daily dose of a CAE substance (presently selegiline is the only available drug) on a higher activity level, thus to fight against the physiological aging-related, slow decay of the catecholaminergic system, is a suitable prophylactic anti-aging measure.[40,49–52]

Knoll has persistently argued, why the discovery of the enhancer sensitivity of the catecholaminergic and serotonergic neurons glimmer just the peak of the iceberg.[52] Even the first developed synthetic enhancers, DEP and BPAP, are not identical in their molecular mechanism.[52,53] Thus, the various forms of natural enhancers capable to increase the excitability of specifically sensitive neurons to a maximum level seem to represent a widely distributed basic mechanism in the mammalian brain. As we have with the aid of DEP and BPAP a fair chance to rapidly recognize unknown enhancer regulations in the mammalian brain, and studies in progress that firmly support this view,[40] this new line of brain research is indeed of great promise.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGMENTS

The author of this paper, one of his coworkers, who was lucky to join his staff 35 years ago and still has the privilege to work with him daily in his lab, congratulates Professor József Knoll, a pioneer of neuro-psychopharmacology, on his 90th birthday. There can be little doubt that Professor Knoll's life work summarized in his monographs[40,52,54] provides the everlasting effort of science to improve the quality and duration of human life with a hopeful new basis.

REFERENCES

1 Knoll J, Ecseri Z, Kelemen K, Nievel J, Knoll B. Phenylisopropylmethyl propinylamine (E-250) a new psychic energizer. *Arch Int Pharmacodyn Ther* 1965; **155**: 154–164.
2 Varga E, Tringer L. Clinical trial of a new type of promptly acting psychoenergetic agent (phenyl-isopropylmethyl-propinylamine HCl, E-250). *Acta Med Acad Sci Hung* 1967; **23**: 289–295.
3 Tringer L, Haits G, Varga E. The effect of (-)E-250, (-)L-phenyl-isopropylmethyl-propinyl-amine HCl, in depression'. In: Leszkovszky G (ed). *V. Conferentia Hungarica pro Therapia et Investigatione in Pharmacologia*. Publishing House of the Hungarian Academy of Sciences: Budapest, Hungary, 1971, pp 111–114.
4 Mann JJ, Gershon S. A selective monoamine oxidase-B inhibitor in endogenous depression. *Life Sci* 1980; **26**: 877–882.
5 Bodkin JA, Amsterdam JK. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. *Am J Psych* 2002; **159**: 1869–1875.
6 Blackwell B. Hypertensive crisis due to monoamine oxidase inhibitors. *Lancet* 1963; **ii**: 849–851.
7 Knoll J, Vizi ES, Somogyi G. Phenylisopropylmethylpropinylamine (E-250), a monoamine oxidase inhibitor antagonizing the effects of tyramine. *Arzneim Forsch* 1968; **18**: 109–112.
8 Elsworth JD, Glover V, Reynolds GP, Sandler M, Lees AJ, Phuapradit P *et al.* Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the 'cheese effect'. *Psychopharmacology* 1978; **57**: 33–38.
9 Sandler M, Glover V, Ashford A, Stern GM. Absence of 'cheese effect' during deprenyl therapy: some recent studies. *J Neural Transm* 1978; **43**: 209–215.
10 Birkmayer W, Riederer P, Ambrozi L. Youdim MBH. Implications of combined treatment with 'Madopar' and L-Deprenil in Parkinson's disease. *Lancet* 1977; **1**: 439–443.
11 Knoll J, Magyar K. Some puzzling effects of monoamine oxidase inhibitors. *Adv Biochem Psychopharmacol* 1972; **5**: 393–408.
12 Birkmayer W, Hornykiewicz O. Der L-dioxyphenyl-alanin-effekt beim Parkinson syndrom des Menschen. *Arch Psychiat Nervenkrh* 1962; **203**: 560–564.
13 Harsing RG, Magyar K, Tekes K, Vizi ES, Knoll J. Inhibition by (-)-deprenyl of dopamine uptake in rat striatum: a possible correlation between dopamine

uptake and acetylcholine release inhibition. *Pol J Pharm Pharmacy* 1979; **31**: 297–307.
14 Knoll J. R-(-)Deprenyl (Selegiline, Movergan^{R}) facilitates the activity of the nigrostriatal dopaminergic neuron. *J Neural Transm* 1987; **25**: 45–66.
15 Knoll J. The striatal dopamine dependency of lifespan in male rats. Longevity study with (-)deprenyl. *Mech Ageing Dev* 1988; **46**: 237–262.
16 Knoll J. Selective inhibition of B type monoamine oxidase in the brain: a drug strategy to improve the quality of life in senescence. In: Keverling Buisman JA (ed). *Strategy in Drug Research*. Elsevier: Amsterdam, Netherlands, 1982, pp 107–135.
17 Knoll J. The facilitation of dopaminergic activity in the aged brain by (-)deprenyl. A proposal for a strategy to improve the quality of life in senescence. *Mech Ageing Dev* 1985; **30**: 109–122.
18 Riederer P, Wuketich S. Time course of nigrostriatal degeneration in Parkinson's disease. *J Neural Transm* 1976; **38**: 277–301.
19 Fowler CJ, Wiberg A, Oreland L, Winblad B. The effect of age on the activity and molecular properties of human brain monoamine oxidase. *J Neural Transm* 1980; **49**: 1–20.
20 McGeer EG, McGeer PL, Wada JK. Distribution of tyrosine hydroxylase in human and animal brain. *J Neurochem* 1971; **18**: 1647–1658.
21 Birkmayer W, Knoll J, Riederer P, Youdim MB, Hars V, Marton J. Increased life expectancy resulting from addition of L-deprenyl to Madopar treatment in Parkinson's disease: a longterm study. *J Neural Transm* 1985; **64**: 113–127.
22 Knoll J, Dalló J, Yen TT. Striatal dopamine, sexual activity and lifespan. Longevity of rats treated with (-)deprenyl. *Life Sci* 1989; **45**: 525–531.
23 Knoll J. The pharmacology of selegiline /(-)deprenyl/. *Acta Neurol Scand* 1989; **126**: 83–91.
24 Carrillo MC, Kanai S, Nokubo M, Kitani K. (-)Deprenyl induces activities of both superoxide dismutase and catalase but not of glutathion peroxidase in the striatum of young male rats. *Life Sci* 1991; **48**: 517–521.
25 Knoll J. Memories of my 45 years in research. *Pharmacol Toxicol* 1994; **75**: 65–72.
26 Knoll J, Yen TT, Miklya I. Sexually low performing male rats die earlier than their high performing peers and (-)deprenyl treatment eliminates this difference. *Life Sci* 1994; **54**: 1047–1057.
27 Tetrud JW, Langston JW. The effect of (-)deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989; **245**: 519–522.
28 Parkinson Study Group. Effect of (-)deprenyl on the progression disability in early Parkinson's disease. *New Eng J Med* 1989; **321**: 1364–1371.
29 Knoll J. Pharmacological basis of the therapeutic effect of (-)deprenyl in age-related neurological diseases. *Med Res Rev* 1992; **12**: 505–524.
30 Knoll J. (-)Deprenyl-medication: a strategy to modulate the age-related decline of the striatal dopaminergic system. *J Am Ger Soc* 1992; **40**: 839–847.
31 Knoll J, Knoll B, Török Z, Timár J, Yasar S. The pharmacology of 1-phenyl-2-propylaminopentane (PPAP), a deprenyl-derived new spectrum psychostimulant. *Arch Int Pharmacodyn Ther* 1992; **316**: 5–29.
32 Miklya I, Knoll B, Knoll J. A pharmacological analysis elucidating why, in contrast to (-)-deprenyl (selegiline) α-tocopherol was ineffective in the DATATOP study. *Life Sci* 2003; **72**: 2641–2648.
33 Miklya I. The Knoll-concept to decrease the prevalence of Parkinson's disease, Chapter 5. In: Finkelstein DI (ed). *Towards New Therapies for Parkinson's Disease*. InTech Open Access Publisher: Rijeka, Croatia, 2011, pp 77–100.
34 Miklya I. Essential difference between the pharmacological spectrum of (-)-deprenyl and rasagiline. *Pharmacol Rep* 2014; **66**: 453–458.
35 Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO study. *Arch Neurol* 2002; **59**: 1937–1943.
36 Knoll J, Tóth V, Kummert M, Sugár J. (-)Deprenyl and (-)parafluorodeprenyl-treatment prevents age-related pigment changes in the substantia nigra. A TV-image analysis of neuromelanin. *Mech Ageing Dev* 1992; **63**: 157–163.
37 Knoll J, Miklya I. Multiple, small dose administration of (-)deprenyl enhances catecholaminergic activity and diminishes serotoninergic activity in the brain and these effects are unrelated to MAO-B inhibition. *Arch Int Pharmacodyn Ther* 1994; **328**: 1–15.
38 Knoll J, Miklya I. Enhanced catecholaminergic and serotoninergic activity in rat brain from weaning to sexual maturity. Rationale for prophylactic (-)deprenyl (selegiline) medication. *Life Sci* 1995; **56**: 611–620.
39 Knoll J, Miklya I, Knoll B, Markó R, Rácz D. Phenylethylamine and tyramine are mixed-acting sympathomimetic amines in the brain. *Life Sci* 1996; **58**: 2101–2114.
40 Knoll J. *How Selegiline /(-)-Deprenyl Slows Brain Aging*. Bentham Science Publishers: E-book, Sharjah, United Arab Emirates, 2012.
41 Martini E, Pataky I, Szilágyi K, Venter V. Brief information on an early phase-II study with (-)deprenyl in demented patients. *Pharmacopsychiatry* 1987; **20**: 256–257.
42 Tariot PN, Cohen RM, Sunderland T, Newhouse PA, Yount D. Mellow AM. L-(-) Deprenyl in Alzheimer's disease. *Arch Gen Psych* 1987; **44**: 427–433.
43 Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *New Eng J Med* 1997; **336**: 1216–1222.
44 Wilcock GK, Birks J, Whitehead A, Evans SJ. The effect of selegiline in the treatment of people with Alzheimer's disease: a meta-analysis of published trials. *Int J Geriatr Psychiatry* 2002; **17**: 175–183.
45 Milgram NW, Ivy GO, Head E, Murphy PM, Wu PH, Ruehl WW *et al.* The effect of L-deprenyl on behavior, cognitive function, and biogenic amines in the dog. *Neurochem Res* 1993; **18**: 1211–1219.
46 Knoll J, Yoneda F, Knoll B, Ohde H, Miklya I. (-)l-(Benzofuran-2-yl)-2-propylaminopentane, [(-)BPAP], a selective enhancer of the impulse propagation mediated release of catecholamines and serotonin in the brain. *Br J Pharmacol* 1999; **128**: 1723–1732.
47 Knoll J, Miklya I, Knoll B. Stimulation of the catecholaminergic and serotoninergic neurons in the rat brain by R-(-)-1-(benzofuran-2-yl)-2-propylaminopentane, (-)-BPAP. *Life Sci* 2002; **71**: 2137–2144.
48 Knoll J, Miklya I, Knoll B, Dalló J. Sexual hormones terminate in the rat the significantly enhanced catecholaminergic/serotoninergic tone in the brain characteristic to the post-weaning period. *Life Sci* 2000; **67**: 765–773.
49 Knoll J. (-)Deprenyl (selegiline) a catecholaminergic activity enhancer (CAE) substance acting in the brain. *Pharmacol Toxicol* 1998; **82**: 57–66.
50 Knoll J. Antiaging compounds: (-)Deprenyl (Selegiline) and (-)1-(benzofuran-2-yl)-2-propylaminopentane, (-)BPAP, a selective highly potent enhancer of the impulse propagation mediated release of catecholamines and serotonin in the brain. *CNS Drug Rev* 2001; **7**: 317–345.
51 Knoll J. Enhancer regulation/endogenous and synthetic enhancer compounds: a neurochemical concept of the innate and acquired drives. *Neurochem Res* 2003; **28**: 1187–1209.
52 Knoll J. *The Brain and Its Self. A Neurochemical Concept of the Innate and Acquired Drives*. Springer: Berlin, Heidelberg, Germany, New York, USA, 2005.
53 Knoll J, Miklya I, Knoll B, Yasusa T, Shimazu S, Yoneda F. 1-(Benzofuran-2-yl)-2-(3,3,3-trifluoropropyl)aminopentane HCl, 3- F-BPAP, antagonizes the enhancer effect of (-)-BPAP in the shuttle box and leaves the effect of (-)-deprenyl unchanged. *Life Sci* 2002; **71**: 1975–1984.
54 Knoll J. *The Theory of Active Reflexes. An analysis of Some Fundamental Mechanisms of Higher Nervous Activity*. Hafner Publishing Company: New York, USA, 1969.