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R-Deprenyl: Pharmacological Spectrum of its Activity

K. Magyar · B. Szende · V. Jenei · T. Tábi ·
M. Pálfi · É. Szökő

Abstract Deprenyl has been discovered by Knoll and
co-workers. The *R*-enantiomer of deprenyl (selegiline) is a
selective and irreversible inhibitor of the B-isoform of
monoamine oxidase (MAO-B) enzyme. Due to its dopa-
mine potentiating and possible neuroprotective properties it
has an established role in the treatment of parkinsonian
patients. By inhibiting MAO-B enzyme, *R*-deprenyl
decreases the formation of hydrogen peroxide, alleviating
the oxidative stress also reduced by increased expression of
antioxidant enzymes (superoxide dismutases and catalase)
reported during chronic treatment. It was shown to prevent
the detrimental effects of neurotoxins like MPTP and DSP-4.
R-Deprenyl elicits neuroprotective and neuronal rescue
activities in concentrations too low to inhibit MAO-B. It is
extensively metabolized and some of the metabolites pos-
sess pharmacological activities, thus their contribution to
neuroprotective properties was also suggested. The recently
identified deprenyl-*N*-oxide is extensively studied in our
laboratory. Effects other than neuroprotection, like influ-
encing cell adhesion and proliferation cannot be neglected.

Introduction

The *R*-enantiomer of deprenyl (phenyl-isopropyl-methyl-
propargylamine; selegiline) is a potent selective, irreversible
inhibitor of the B-form of monoamine oxidase (MAO-B)
enzyme [37, 48]. The first paper about the pharmacological
properties of deprenyl was published in 1965, by Knoll and
his co-workers [38]. The primary aim to synthesize MAO
inhibitors, in the late fifties and early sixties, was to
develop antidepressive agents. The new inhibitors became
potent antidepressants, but all of them, except *R*-deprenyl
[39], potentiated the effect of tyramine, and elicited
hypertensive crisis, the so called "cheese-effect" [12, 61].
Birkmayer and his co-workers described, that *R*-deprenyl
potentiated the effects of dopamine [8–11] and during the
last three decades, from among MAO inhibitors, it became
the drug of choice to treat Parkinson's disease. *R*-deprenyl
in a daily oral dose of 5–10 mg inhibited oxidative
deamination of dopamine, as well as the age-dependent
increase of MAO-B activity [1, 59, 68]. By reducing the
formation of hydrogen peroxide (H_2O_2), *R*-deprenyl
decreases the oxidative damage caused by the formation
reactive oxygen species (ROS). Chronic treatment of rats
with *R*-deprenyl was found to stimulate the expression of
antioxidant enzymes, such as superoxide dismutases
(SOD1, SOD2) and catalase [13] in the brain, which can
neutralize the excessive amount of ROS.

Many papers published that *R*-deprenyl in a concentra-
tion too low to inhibit MAO-B activity, affects some
neuronal and extraneuronal functions; such as cellular
signaling pathways, antiapoptotic mechanisms, trophic

K. Magyar (✉) · T. Tábi · M. Pálfi · É. Szökő
Department of Pharmacodynamics, Semmelweis University,
H-1445, Budapest, POB 370, Hungary
e-mail: kalman.magyar@net.sote.hu

K. Magyar
Neurochemical Research Unit, Hungarian Academy of Sciences,
Budapest, Hungary

B. Szende
1st Department of Pathology and Experimental Cancer Research,
Semmelweis University, Budapest, Hungary

V. Jenei
Chemical Research Center, Hungarian Academy of Sciences,
Budapest, Hungary

effects, cell to cell adhesion etc. [50, 88, 89]. Many of these are extra-neural and non-central processes. It was published in 2005 by Jenei et al. [31] from our laboratory, that R-deprenyl decreases cell–cell adhesion. It was postulated, that in addition to adhesion, chemotaxis elicited by biologically active ligands, might also be an important component of R-deprenyl's effects.

During the last decade it was revealed in many laboratories including ours [45], that not only the parent compound, but also its metabolites are responsible for the broad-spectrum of pharmacological activities of R-deprenyl. It seemed reasonable to enroll the metabolites into the pharmacological studies.

Beside R-deprenyl, a new selective inhibitor of MAO-B, named rasagiline has been discovered. Pre-clinical and clinical studies revealed its therapeutic usefulness in the treatment of parkinsonian patients. The effects of rasagiline not related to MAO-B inhibition were compared to that of deprenyl [110, 111].

Pharmacokinetic Characteristics of R-Deprenyl

Deprenyl is an optically active compound, where the enantiomers have different pharmacological activity and/or potency. The R-isomer of deprenyl, also called selegiline, was proved a more potent enzyme inhibitor than its antipode [48].

R-deprenyl is quickly and well absorbed from the gastrointestinal tract, [4, 28, 29, 43, 47, 52, 53, 75], the maximum plasma concentration is reached within 0.5 and 1.5 h after oral administration [29, 47, 75]. R-deprenyl has considerable *first pass* metabolism [4, 28, 52, 54, 56], the biological availability was found 4% in humans [2]. Concomitant food consumption has increased the absorbed amount of R-deprenyl by about three times, without changing the plasma concentration of its metabolites [5]. Since the parent compound is responsible for the inhibition of MAO-B enzyme, there is a considerable difference in the brain enzyme activity following oral or parenteral drug administration [25]. Recently, orally disintegrating dosage form of R-deprenyl has been developed, avoiding *first pass* metabolism. This formulation provides higher drug bioavailability, and considerably reduced metabolite concentration [14, 63]. Percutaneous absorption of R-deprenyl is also favorable [6, 7, 23, 69], and as its cutaneous metabolism is insignificant [70], transdermal application provides about 50-fold higher plasma concentration compared to oral drug administration [6]. According to this higher concentration, considerable inhibition of MAO-A activity in the brain is also achieved, while the intestinal MAO-A activity is only slightly affected. This way R-deprenyl does have antidepressant activity without a significant risk of "cheese-effect" [21, 105].

Autoradiographic studies in mice revealed rapid distribution of R-deprenyl. High concentration was detected in lipid-rich tissues, like in the brain, 30 s after *i.v.* administration. The concentration then dropped rapidly in the brain, while increased in the parenchymal tissues [43]. The main metabolites: methamphetamine (MA) and amphetamine (A) were identified in the brain of the animals after intraperitoneal [62] and subcutaneous [34, 58] administration of R-deprenyl. These metabolites were also detected *post mortem* in various brain regions of treated parkinsonian patients [66]. In the experiments performed in our laboratory, using dual-labeled R-deprenyl, both ^{14}C-propargyl, indicating the parent compound, and ^{3}H-phenyl, indicating all metabolites were detected in plasma and various brain regions. Both type of radioactivity showed accumulation after repeated drug administration. Steady state concentration of the compounds with or without propargyl group was reached after 4 and 7 days, respectively both in plasma and striatum, the primary site of action [43, 49, 51]. According to the results of positron emission tomography studies with ^{11}C-labeled deprenyl, the enantiomers do not differ in their early phase tissue distribution, as both isomers penetrate quickly to the brain and other tissues. However, the excretion has shown considerable stereoselectivity, as R-deprenyl accumulated significantly in tissues containing high MAO-B activity, such as in the brain, heart and lung. In case of its antipode (S-deprenyl) rapid, exponential decline in the brain, similarly to MA, was observed. The persistent and high radioactivity in the brain can be explained by the irreversible binding of R-deprenyl to MAO-B enzyme [22, 30], confirmed by investigations performed using knock-out mice [19]. The autoradiography studies have shown binding primarily in subcortical parts of the brain, which is rich in MAO-B according to previous studies [17, 40], while the cortex and the white matter was almost lack of radioactivity [32].

Since determination of the pharmacokinetic parameters of R-deprenyl was difficult because of its low plasma concentration due to considerable *first pass* metabolism and rapid tissue distribution, in early bioequivalence studies plasma concentrations of the main desalkylated metabolites, MA and desmethyldeprenyl (DD) instead of the parent compound were compared in case of the various preparations [57, 60]. In 1994 Mahmood et al. [55] have developed a sensitive fluorimetric method for determination of R-deprenyl concentration in plasma. Since the procedure is based on the inhibition of MAO enzyme, the presence of the metabolites does not disturb the measurement. This method was used for determination of pharmacokinetic parameters of R-deprenyl in dogs after its oral administration. The results have shown rapid absorption ($t_{max} = 25 \pm 5.8$ min), large volume of distribution (6.56 ± 0.56 l/kg), rapid

elimination ($t_{1/2} = 60.24 \pm 9.56$ min) and low bioavailability ($8.51 \pm 3.31\%$) [54]. Similar results have been found in human experiments, maximum plasma concentration was reached within 0.5 and 1.5 h after drug ingestion, the elimination half-life was 70 min. There was no considerable difference in the pharmacokinetic parameters when *R*-deprenyl was administered orally as a tablet or as a solution [56]. Intensive metabolism in the liver and extra-hepatic organs was suggested based on the high oral clearance found in human experiments [53]. Slight accumulation of the parent drug and the metabolites was observed after repeated doses. Elimination half-life of deprenyl and DD was increased by 3–6 times compared to single dose administration, with less variability of the pharmacokinetic parameters [5].

Metabolism and Excretion of *R*-Deprenyl

Early metabolism studies have revealed the formation of MA and A by desalkylation, and urinary excretion of these metabolites in high amounts in humans [28, 67, 73], and rats [41, 47, 80, 108]. DD was also detected in urine, although in much lower concentration than A derivatives [28, 41, 73, 80].

The amphetamines are pharmacologically active metabolites, and the enantiomers possess considerably different psychostimulant effect; the *S*-isomers being much stronger inhibitors of noradrenaline and dopamine transporters, than *R*-amphetamines [93]. The stereoselective effect of deprenyl and its metabolites required studying the stereochemistry of the metabolism. Schachter et al. [71] published first the stereoselective nature of desalkylation. In our laboratory chiral capillary electrophoresis methods were developed for the enantiomeric separation of deprenyl and amphetamine derivatives [79], and we have proved the stereospecific desalkylation of both *R*- and *S*-deprenyl in rats. In the urine [80], plasma and tissue samples of animals treated with *R*-deprenyl [81, 82], only *R*-A derivatives were identified, while only *S*-A derivatives were found in specimens from rats treated with *S*-deprenyl; no racemization or inversion happened during metabolism. The stereospecific nature of the metabolism was also confirmed by Shin analyzing urine samples of healthy volunteers [73]. There is some controversy about the various CYP isoforms desalkylating selegiline. CYP 2D6 [3, 24], CYP 3A4 [18, 85] and CYP 2E1 [103] were found to be involved in the formation of MA and DD. The possible role of flavin-containing-monooxygenase (FMO) enzymes in the formation of A was also suggested [109].

Desalkylated metabolites can be further converted by hydroxylation of the benzene-ring at *para*-position, or by hydroxylation of the alkyl chain at β-position. High amount of *para*-hydroxylated amphetamine derivatives were excreted in the urine of rats treated with selegiline [33, 41, 108], and were also identified in human urine, although in somewhat lower concentration [73, 87]. Small amount of *para*-hydroxy-DD was also found in rat urine [33]. Majority of the *para*-hydroxylated metabolites were excreted as conjugates [73].

Ephedrine derivatives can also derive by the β-hydroxylation of the alkyl chain. Ephedrine and pseudoephedrine can be formed from MA, while norephedrine and nor-pseudoephedrine from A. These β-hydroxylated metabolites could be identified in the urine of volunteers treated with *R*-deprenyl, but their total amount was less than 1% of the applied dose [73]. In the pharmacokinetic studies performed in our laboratory, no ephedrine derivatives could be observed in urine of rats treated with *R*- or *S*-deprenyl [80]. Beside desalkylation, the possibility of another metabolic pathway was recently suggested by Wu and Ichikawa. In their in vitro experiments, competitive inhibition of FMO-catalyzed metabolism of MPTP by deprenyl and pargylin was observed. Based on their results, these MAO inhibitors are substrates of FMO by themselves, and the formation of *N*-oxide metabolites from the *tertiary*-amines was supposed [107]. Previously, highly sensitive and efficient gas-chromatographic methods were used for the wide-spread pharmacokinetic studies of *R*-deprenyl. However, these were not capable of detecting the *N*-oxide metabolites, because of the high temperature and sample derivatization needed for the separation, inducing decomposition of the *N*-oxide. In early thin-layer chromatographic studies of selegiline metabolism, in addition to the desalkylated derivatives, an unidentified metabolite was also observed, but it could not be detected by gas-chromatography [46]. This detected but unidentified metabolite could be deprenyl-*N*-oxide (DNO). Recently, in vivo formation of *N*-oxide metabolite from *R*-deprenyl in humans was shown by HPLC and HPLC–MS methods [35, 36] and its in vitro production by liver microsomal preparations [42, 102] was also demonstrated. The known metabolic pathways of selegiline are shown in Fig. 1.

Oxidation of the tertiary prochiral nitrogen of deprenyl provides quaternary nitrogen, a new chiral center. DNO thus contains two asymmetry centers and its four diastereomers (i.e. two pairs of enantiomers) exist. Each isomer has one enantiomer and two diastereomers among the other isomers (Fig. 2). The metabolic transformation of *R*-deprenyl can lead to the generation of *1R,NR*- and *1R,NS*-DNO, while *S*-deprenyl can be converted to *1S,NR*- and *1S,NS*-DNO. Since DNO is supposed to contribute to the pharmacological effects of *R*-deprenyl, the in vivo formation of the isomers was also studied in our laboratory [86].

The analysis of the urine samples of rats treated with either *R*- or *S*-deprenyl orally revealed that the new chiral centre on the quaternary nitrogen atom was formed

Fig. 1 Metabolic pathway of
R-(—)-deprenyl
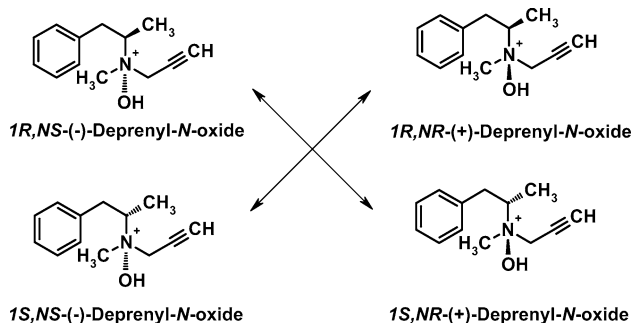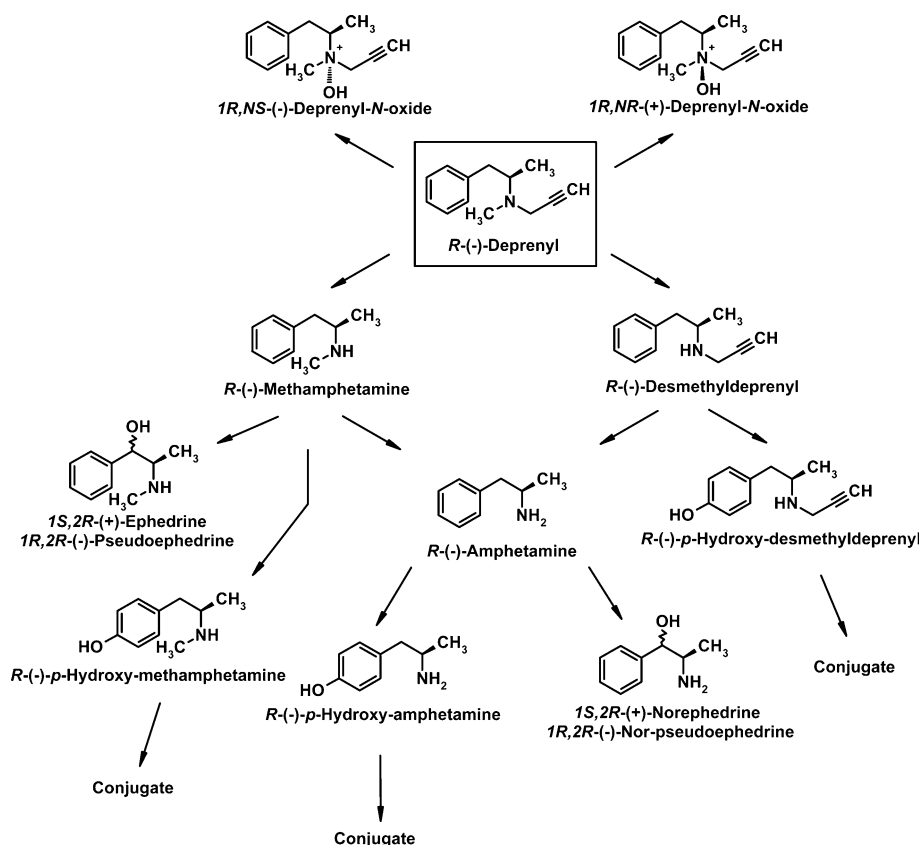
Fig. 2 Isomers of deprenyl-*N*-oxide

stereoselectively, where the configuration of *S*- over the *R*- was preferred. *1R,NS*- and *1S,NS*-isomers were formed in 3–5 fold excess compared to *1R,NR*- and *1S,NR*-isomers in rats during in vivo metabolism of *R*- and *S*-deprenyl, respectively. Based on our in vitro metabolism studies, FMO1 enzyme is responsible for the stereoselective formation of *NS*-isomers, while FMO3 preferentially forms the *NR* configuration. Using microsomal preparation, much lower enantioselectivity was observed, indicating, that CYP enzymes do not show stereoselectivity in the formation of the new chiral centre on the quaternary nitrogen [83]. Our results of stereoselective *N*-oxide formation are in accordance with previous findings [26, 27] with pargylin, a non-selective MAO inhibitor having similar structure

to deprenyl, where highly stereoselective and species-dependent *N*-oxide production was found [26].

In our in vivo metabolism experiments rats were treated with a single dose of *R*-deprenyl, and the metabolites excreted in the urine were identified. The amount of DNO, excreted in rat urine collected during 24 h after treatment represented 1–5% of the dose administered. Majority of *N*-oxide metabolite was found in the fraction of urine collected 0–3 h after single dose drug administration, when its amount was comparable to that of MA and A. After 9 h following treatment, increasing amounts of *para*-hydroxylated derivatives were detected in the urine, while the excretion of DNO decreased. Considerable amounts of A and MA were found in all urinary fractions. DD and parent compound could be detected only in low amounts in the urine [84]. When repeated dose of *R*-deprenyl was administered to rats, 55–75% of the dose was recovered in urine 24 h after the last treatment. After repeated drug administration, the amounts of the *para*-hydroxylated desalkylated metabolites increased in the urine, and became the most abundant metabolites excreted. The total amount of the *para*-hydroxylated compounds in the urine has reached 50–60% of the dose administered, the majority (50–67%) of which were identified as conjugate. The amount of the parent compound in the urine slightly increased after repeated drug administration (from 0.3 to

2% of the dose), while that of DNO decreased (below 1% of the dose). The amount of DD was very low in all the urine samples (0.01–0.4% of the dose) [84].

When a single dose of diastereomeric mixture (1:1) of deprenyl-N-oxides (5 mg/kg) was administered orally to rats, more than 60% of the dose was excreted unchanged in the urine during 3 h following treatment, and further 10% until 24 h (Fig. 3a). About 10% of the dose was identified as metabolites (R-deprenyl, DD, MA, A, para-hydroxy-MA, para-hydroxy-A, para-hydroxy-DD) in the urine during 24 h after treatment. The urinary excretion of the metabolites formed from DNO within 24 h after its administration is shown in Fig. 3b. The conjugated metabolites were not determined in this experiment. These data indicate that some of the DNO is reduced to deprenyl in rats, and further metabolised by desalkylation and aromatic hydroxylation. This finding also raises the possibility of retro-reduction of DNO metabolite to the parent compound in case of R-deprenyl treatment. Previously, the reduction of N-hydroxylamines by benzamidoxime reductase and human liver microsomes to their parent amines has been demonstrated [15]. This reduction mechanism may

also apply in case of N-oxide metabolites formed from tertiary amines.

The Neuroprotective and Neuronal Rescue Effect of *R*-Deprenyl and Some of its Metabolites

Starting at 1994 Tatton et al. published that R-deprenyl in a concentration too low to inhibit MAO-B activity (10^{-9}–10^{-13} M) reduces apoptosis by inducing new protein synthesis. This fact was first made evident by the results of in vitro studies by Tatton et al. [89], who pointed out using in vitro cultured partially NGF-differentiated PC-12 cells of neuroectodermal origin that R-deprenyl prevents apoptosis-inducing effect of serum and nerve growth factor deprivation in such a low dose (10^{-9} mol/l), which does not exhibit MAO-B inhibitory action. As previous results drew the attention to neuronal apoptosis as likely to be responsible at least in part for cell death in Parkinson's disease, Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis, drugs with antiapoptotic, neuroprotective characteristics seem to be promising candidates for future therapy.

R-Deprenyl has been demonstrated to prevent or diminish the effect of various apoptosis-inducing damaging factors both in vitro and in vivo. These factors include serum deprivation, glutathion depletion, poisoning with excitotoxins, okadaic acid, nitric oxide, peroxynitrite, cytosine arabinoside, as well as peripheral nerve crush and axotomy [91].

The anti-apoptotic effect of R-deprenyl has been investigated by our group [44, 45, 50, 51, 76–78] using the human melanoma cell line A2058. Melanocytes are of neuroectodermal origin, like phaeochromocytoma cells used by Tatton et al.; however, our cultures had not been differentiated by NGF, which could account for the discrepancies between the results of the two groups. Serum withdrawal for 5 days resulted in an excessive number of apoptotic cells of the cell cultures, proven by observation of HE-stained cover-slip adherent cultures, TUNEL reaction, flow cytometry and caspase 3 determination [78].Very low doses of R-deprenyl—as given in Tatton's articles [89, 91] i.e. 10^{-7}–10^{-13} mol/l—caused a 48 h delay in the onset of apoptosis in case of serum withdrawal, compared to the untreated control (Table 1). However, the same concentrations of S-deprenyl were ineffective. The effect of higher doses of R-deprenyl (10^{-4}–10^{-2} mol/l) was studied using A2058 melanoma and HT 1080 fibrosarcoma cell lines [77]. The cells were grown in serum supplemented MEM, administration of R-deprenyl was performed 2 h after plating. R-Deprenyl administered at a concentration of 10^{-2} mol/l resulted in 100% apoptotic cell death of A2058 cells, while 10^{-3} mol/l R-deprenyl caused apoptosis of 50%
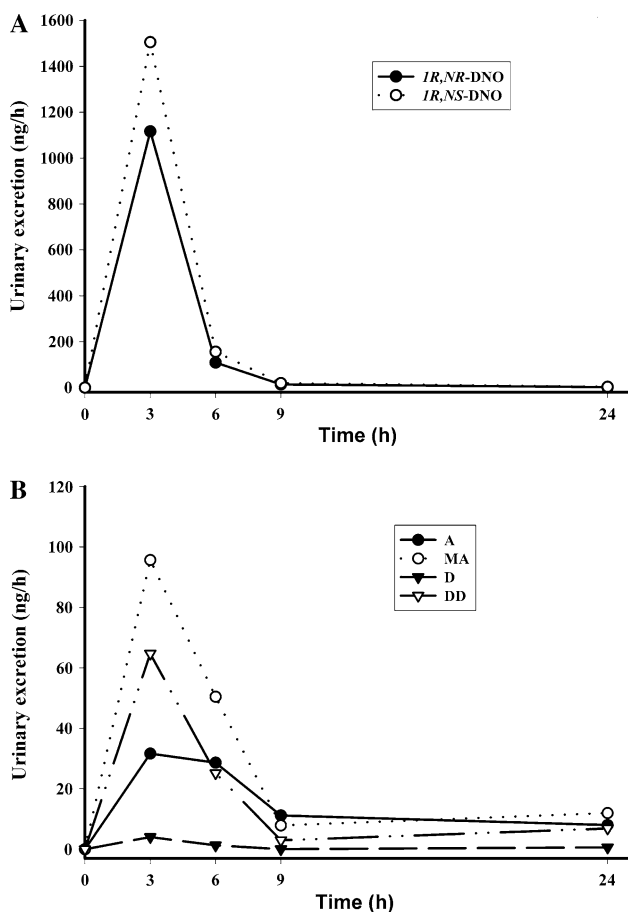

Fig. 3 Urinary excretion of deprenyl metabolites after treatment with deprenyl-N-oxide

Table 1 Effect of various concentrations of R-deprenyl, R-desmethyldeprenyl, R- and S-methamphetamine, SKF-525A and SKF-525A + deprenyl on apoptotic index of serum-deprived A2058 human melanoma cell culture

Days		R-deprenyl in M					R-desmethyl-deprenyl in M			
		0	10^{-3}	10^{-7}	10^{-9}	10^{-13}	10^{-3}	10^{-7}	10^{-9}	10^{-13}
1	Mean	32.34	34	25	7.67	4.67	34.34	35.33	36	35
	±SD	2.52	2	2.65	1.53	0.58	1.53	0.6	3.61	5.20
			NS	$P < 0.05$	$P < 0.001$	$P < 0.001$	NS	NS	NS	NS
2	Mean	42.67	45	35	9.67	8.34	43	44.67	44.67	45
	±SD	2.52	3	1	0.58	1.16	1.73	2.08	2.52	2
			NS	$P < 0.01$	$P < 0.0001$	$P < 0.0001$	NS	NS	NS	NS
3	Mean	84	79	57.67	13.67	13	80.67	81.34	81	82.67
	±SD	3.61	3.61	2.52	1.53	1	3.79	2.08	1	0.58
			NS	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	NS	NS	NS	NS

Days		R-methamphetamine in M					S-methamphetamine in M			
		0	10^{-3}	10^{-7}	10^{-9}	10^{-13}	10^{-3}	10^{-7}	10^{-9}	10^{-13}
1	Mean	32.34	33.67	35.34	33	34	33.67	33.34	33	33.33
	±SD	2.52	0.58	3.06	2.65	1.73	3.22	1.16	2	2.3
			NS	NS	NS	NS	NS	NS	NS	NS
2	Mean	42.67	41	43.67	43	46.67	48	46	46.34	43.34
	±SD	2.52	1	0.58	1	1.53	1	1	2.08	3.06
			NS	NS	NS	NS	NS	NS	NS	NS
3	Mean	84	82	81	81.66	81	82	80.33	81.33	82.33
	±SD	3.61	2.64	1.73	2.08	1	1.73	2.51	2.08	1.52
			NS	NS	NS	NS	NS	NS	NS	NS

Apoptotic index (%)

Days		Control	SKF-525A 10^{-4} M	SKF-525A 10^{-4} M + R-deprenyl 10^{-9} M	SKF-525A 10^{-4} M + R-deprenyl 10^{-13} M
1	Mean	32.34	32.67	34	34.67
	±SD	2.52	1.16	1.73	1.16
			NS	NS	NS
2	Mean	42.67	42	43	43
	±SD	2.52	2.65	2.65	1
			NS	NS	NS
3	Mean	84	82	84	81.67
	±SD	3.61	2	2	2.08
			NS	NS	NS

$n = 3$; NS = not significant

of the melanoma cells. Very similar results were published by Tatton et al. [91] after 10^{-3} mol/l R-deprenyl treatment of PC-3 cells. Administration of 10^{-4}–10^{-3} mol/l R-deprenyl to HT 1080 fibrosarcoma cell cultures induced apoptosis dose-dependently. However, 10^{-2} mol/l R-deprenyl caused cytoplasmic, vacuolar, non-lysosomal cell death 24, 48 and 72 h after administration [77].

As mentioned above, 10^{-7}–10^{-13} mol/l R-deprenyl temporarily prevented apoptosis of A2058 cells after serum deprivation. Simultaneous administration of the non-specific microsomal drug metabolising enzyme inhibitor SKF-525A with R-deprenyl abolished the anti-apoptotic effect [45]. This could mean that R-deprenyl needs metabolic changes in order to exert its anti-apoptotic activity. However, the pro-apoptotic effect of higher doses (10^{-3}–10^{-4} mol/l) of R-deprenyl could not be influenced by SKF-525A, indicating that R-deprenyl itself and not its metabolites exert pro-apoptotic activity. Nevertheless, it is more reasonable to assess the metabolism of deprenyl directly if in vitro models are used, as it may differ significantly from metabolism in vivo. This has been demonstrated by our group using undifferentiated PC-12 cells,

where deprenyl did not undergo any metabolic changes in this culture during the 3 days of experiment (unpublished results). Furthermore, SKF-525A may also possess proapoptotic effects, hindering the interpretation of the results.

Regarding metabolites of R-deprenyl R-DD, MA, A are the best known [36, 73]. DNO became also a possible candidate for being the ultimate effector molecule [75]. Our studies are in progress in this respect.

According to Tatton et al. [88] MA and A did not alter the survival of trophically withdrawn PC-12 cells. Similar result has been found by our group using 10^{-7}–10^{-13} mol/l R-MA- or S-MA-treated serum deprived A2058 melanoma cells. Although R-DD was supposed to be the active metabolite of R-deprenyl [89], our results on serum-deprived A2058 cells showed no anti-apoptotic effect of low doses of DD [77] (Table 1). High doses of DD (10^{-2}–10^{-4} mol/l) caused death of A2058 melanoma and HT 1080 fibrosarcoma cells. In vivo, 2058 human tumor xenografts, when treated by 0.2–20.0 mg/kg DD, showed dose-dependent growth inhibition [77].

Experiments regarding the anti-apoptotic effect of low doses of R-deprenyl using non-neuronal cells led to different results according to the origin of such cells. Studies on mouse thymocytes [20] showed that R-deprenyl did not exhibit detectable protective effect after dexamethasone treatment which induced apoptosis. On the other hand, it has been proven by our group, that R-deprenyl diminished the apoptosis-inducing effect of ischaemia–reperfusion in experimental rats [101]. The most effective dose was 0.15 mg/kg which equals the human therapeutic dose applied in neurodegenerative disease. Qin and his co-workers [64] reported that R-deprenyl may be a potent inhibitor of non-neuronal apoptosis also in case of cardiac tissue.

The possible mode of apoptosis inhibitory action of R-deprenyl has been widely discussed. R-Deprenyl treatment might protect neurons from oxidative damage mediated by lipid peroxydation of the cell membrane [74], by reducing the production of H_2O_2 due to inhibition of the normal metabolism of dopamine by MAO-B [16].

As mentioned earlier, R-deprenyl can also increase neuronal survival without inhibiting MAO-B. The mechanism of the established anti-apoptotic property of R-deprenyl is most likely achieved through modulation of gene expression interfering with the apoptotic cascades, preferably the mitochondrial pathway. Regarding this pathway, apoptosis is mediated by loss of mitochondrial membrane potential inducing the opening of the mitochondrial membrane permeability transition pore, leading to a release of pro-apoptotic factors such as cytochrome C and apoptosis-inducing factor (AIF). Activation of the pro-apoptotic protein BAX cause decrease in mitochondrial membrane potential, whereas the maintenance of mitochondrial membrane potential is strongly supported by

increased activity of BCL2. Studies of Tatton and others [65, 88, 90, 104] point to the fact, that R-deprenyl alters the expression of these genes in the course of apoptosis in favor of stabilization of mitochondrial membrane potential.

The Effect of R-Deprenyl Outside the Central Nervous System

R-Deprenyl has been shown to affect a number of functions which could explain its beneficial effect in Parkinson's disease. These functions include its MAO-B inhibitory effect, modulation of cellular signaling pathways, such as pro- and anti-apoptotic pathways, redox signaling or trophic effects of the drug. Although most publications focus on the neuroprotective functions of R-deprenyl, a small but increasing number of publications are discussing its beneficial effects outside the central nervous system. Thyaga Rajan et al. [97–100] in several studies examined the anti-tumor effects of R-deprenyl in rats with either spontaneously growing or carcinogen-induced mammary/pituitary tumors. In old, acyclic female rats treatment with R-deprenyl was shown to temporarily re-establish estrous cycles and significantly reduce the incidence of both mammary and pituitary tumors [98]. R-Deprenyl also reduced the number and size of carcinogen-induced mammary tumors by enhancing splenic IL-2, IFN-γ production, NK cell activity and cathecholaminergic neuronal activities of the central and peripheral nervous system [97, 99, 100]. The effect of R-deprenyl on the neuroendocrine-immune network was discussed in an earlier review [96].

A MAO-B-independent anti-apoptotic effect of R-deprenyl has been shown in a number of tumorigenic cell lines, which further suggests that the effect of the drug cannot be limited to the CNS or cells of neural origin. Interestingly, Seymour and co-workers showed that R-deprenyl was specifically protective in non-malignant human cells (HaCat spontaneously immortalized keratinocytes, normal human urothelial explants) versus tumor cells (H-ras-transfected HaCat cells, HPV16 virus-infected HPV-G keratinocyte cell line, PC-3 prostate adenocarcinoma cell line) against the toxic effects of cobalt-60 gamma ionizing radiation and cisplatin [72]. Although the two studies both used cancer cell lines both the choice of cell lines and the induction of apoptosis was different which could explain why R-deprenyl was protective in certain cancer cell lines against apoptosis but not in others. R-Deprenyl was also shown to protect rat kidney against the apoptosis-inducing effect of ischemia–reperfusion [101], the vascular endothelium from the toxic effects of amyloid-beta peptide [95] and it also reduces myocyte apoptosis in vivo [64].

A novel, also MAO-B-independent effect of R-deprenyl on cell–cell adhesion was described by our research group

which could contribute to its protective actions for example in tumour development or neurodegeneration [31]. *R*-Deprenyl significantly increased cell–cell adhesion of NGF-naïve and NGF-differentiated PC-12 cells (of neuro-ectodermal origin) and also NIH3T3 mouse embryonal fibroblasts (non-neuronal) in a concentration-dependent manner. The effective concentration range which induced cell–cell adhesion in PC-12 cells was slightly higher (10^{-7} M in NGF-naïve and 10^{-9} M in NGF-differentiated PC-12 cells) than its anti-apoptotic concentrations (10^{-11} M in PC-12, 10^{-13} M in melanoma) [78, 92]. Furthermore the anti-apoptotic actions of *R*-deprenyl were only limited to NGF-differentiated PC-12 cells [92] which suggest a different mechanism of the two effects. Microsomal metabolism of *R*-deprenyl is required for its anti-apoptotic effects [78, 90] while inhibition of cytochrome P450 had no effect on its cell–cell adhesion increasing function. Interestingly a rarely studied metabolite of *R*-deprenyl—DNO produced by FMO—was equally effective as the original compound [31].

Very recently two studies reported the inhibitory effect of *R*-deprenyl on hyperpermeability of vascular endothelial cells caused by burn or hemorrhagic shock [94, 106]. The authors attribute the protective effects of the drug to its antioxidant actions, maintenance of mitochondrial membrane potential, inhibition of cytochrome C release from the mitochondria and inhibition of caspase 3 activation. Interestingly, the authors describe reduced intercellular adhesion as part of the mechanism of hyperpermeabilty. Furthermore, they also mention that apoptosis might contribute to these loosening intercellular junctions and cell–matrix adhesions, therefore leading to the detachment of endothelial cells from the underlying basement membrane. Both studies hypothesize that *R*-deprenyl acts by antagonizing apoptosis in these cells, therefore preventing disruption of intercellular junctions caused by apoptosis. Unfortunately, the effect of *R*-deprenyl on endothelial cell–cell adhesion was not studied in these papers [94, 106]. Their hypothesis, however, is very well supported by our finding that *R*-deprenyl actively enhances cell–cell adhesion [31]. The direct effect of *R*-deprenyl on cell–cell adhesion might have contributed to its inhibitory effects on hyperpermeability in vascular endothelial cells. The concentrations used in the aforementioned papers in vitro were (10^{-6}–10^{-5} M) certainly within the concentration range of our cell aggregation experiments where we observed significant increase of cell–cell adhesion in PC-12 or NIH3T3 cells (10^{-9}–10^{-5} M or 10^{-11}–10^{-5} M, respectively) [31]. As the authors in these papers did not test the effects of *R*-deprenyl metabolites on vascular hyperpermeability it is difficult to speculate on any further similarities or differences between the two mechanisms.

Although more investigation is required to clarify the effects of *R*-deprenyl outside the central nervous system the above results suggest that *R*-deprenyl might be more than an agent against Parkinson's disease.

Conclusions

R-Deprenyl is an original Hungarian drug, which has been discovered by Knoll and his co-workers and during the past three decades it was used to treat the disabling Parkinson's disease. *R*-Deprenyl (selegiline) has been the only selective, irreversible MAO-B inhibitor, which in an oral dose of 10 mg/day delays the need for levodopa administration. It proved to be effective even in monotherapy, when it was administered at the early stage of the disease, and its effectiveness lasts till functioning neurons exist in the CNS. Recently, a new MAO-B inhibitor, rasagiline was introduced to therapy. The question arises, whether there is a need for two MAO inhibitors in the treatment of Parkinson's disease. According to our knowledge, the answer is yes, but not because of their different MAO inhibitory effects, but due to the other versatile pharmacological properties of the molecules. Both selegiline and rasagiline in a concentration too low to inhibit the enzyme activity distinctly modify the regulation of apoptotic cascades. The metabolism of selegiline is rather intensive. It has high capacity "first pass" metabolism and the microsomal enzymes convert it to amphetamine, methamphetamine, desmethyldeprenyl, para-hydroxy metabolites and the conjugates of the formers. In addition, the flavin-containing monooxygenase synthesizes deprenyl-*N*-oxide, which has two chiral centers, thus exists in the forms of four enantiomers. Additionally, deprenyl-*N*-oxide has a quaternary character, which alters membrane penetration. As *N*-oxides, it can be reduced back to the parent compound. Both selegiline and its metabolites can elicit diverse pharmacological activities, which play a role in the complex effects of selegiline. *R*-Deprenyl significantly increased cell–cell adhesion of NGF-naive and NGF-differentiated PC-12 cells of neuro-ectodermal origin. Parenteral administration increases the bioavailability of selegiline and the same dose, which is used for oral treatment, effectively inhibits the brain MAO-A enzyme; by overcoming "first pass" metabolism, antidepressive activity can be elicited. Deprenyl-*N*-oxide, the metabolite of selegiline possessing propargyl group also modifies the function of apoptotic cascades. The effect of deprenyl-*N*-oxide is under further studies in our laboratory, and it was found to increase mitotic activity. The mechanisms of the pleiotropic effects of MAO-B inhibitors are thus worth for further studies to understand their complex pharmacological effects.

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