USE OF THE SYNTHETIC ENHANCER SUBSTANCES 
(-)-DEPRENYL AND (-)-BPAP IN MAJOR DEPRESSION

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SUMMARY
There is still a great need for the development of antidepressants with a new pharmacological spectrum. The finding that phenylethylamine and tryptamine are endogenous enhancers of the impulse propagation mediated release of catecholamines and serotonin in the brain, and the development of synthetic mesencephalic enhancer substances opened the possibility to stimulate catecholaminergic and serotonergic neurons in the mesencephalon via a previously unknown mechanism. (-)-Deprenyl, a prototype of the phenylethylamine-derived synthetic enhancer substances, stimulates the catecholaminergic neurons in the brain but is almost ineffective on the serotonergic neurons. R-(-)-1-(benzofuran-2-y1)-2-propylaminopentane, (-)-BPAP, the recently developed tryptamine-derived selective synthetic mesencephalic enhancer substance, a hundred times more potent compound than (-)-deprenyl, acts also on the serotonergic neurons. The evaluation of the peculiar pharmacological profile of the synthetic mesencephalic enhancer substance, especially the high potency and the unusual safeness and the tolerability of (-)-BPAP cherish the hope that this compound may in the future significantly improve the effectiveness of drug therapy in major depression and its combination with uptake inhibitors may substantially diminish the number of therapy resistant cases.

KEYWORDS: antidepressants, mesencephalic enhancer regulation, endogenous mesencephalic enhancer substances, -phenylethylamine (PEA), tryptamine, (-)-deprenyl, (-)-BPAP

ABBREVIATIONS
PEA= -phenylethylamine
(-)-BPAP=R-(-)-1-(benzofuran-2-y1)-2-propylaminopentane
(-)-PPAP= (-)-1-phenyl-2-propylaminopentane
MAO=monoamine oxidase
SSRIs=selective serotonin reuptake inhibitors
DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, version IV-Text Revision
SNRIs=serotonin and noradrenaline reuptake inhibitors
NRIs=noradrenaline reuptake inhibitors
SARIs=serotonin 2A antagonist and reuptake inhibitors

SZINTETIKUS ENHANCER ANYAGOK:
(-)-DEPRENYL ÉS (-)-BPAP MAJOR DEPRESSZIÓBAN

A mai használatos antidepresszívumok széles spektrumáról ad áttekintést és írja le az endogén enhancer phenylethylamin és tryptamin hatását az agyi catecholeminokra és szerotoninra, ezen keresztül az antidepresszívumok hatásmechanizmusának kevésbé ismert, de fontos hipotéziséről beszél. A (-)-deprenyl, mint szintetikus phenylethylamin derivátum, ill. a R-(-)-1-(benzofuran-2-y1)-2-propylaminopentan, (-)-BPAP szintetikus tryptamin derivátum szelektív mezenkefal on enhancer anyagok; a (-)-BPAP százszor hatékonyabb, mint a (-)-deprenyl, hatásos a szerotoninerg neuronokon is. A (-)-BPAP farmakológiai profilja, az igen intenzív mezenkefal on enhancer tevékenysége alapján feltételezhető jó terápiás hatása major depresszióban, így a terápia-rezisztens esetekben is.

KULCSSZAVAK: antidepresszívumok, a mezenkefalon enhancer szabályozása, endogen mezenkefalon enhancer anyagok, -phenylethylamin (PEA), tryptamine, (-)-deprenyl, (-)-BPAP
INTRODUCTION

Therapy of mood disorders such as depression has always been an important field of medicine. In recent decades the world-wide observed marked increase in the prevalence of depression, and its consequence, growing number of suicidal attempts and suicides, caused serious concern (Angst and Dobler-Mikola, 1995; Bauer et al. 2002). To curb this trend needs concerted social and medical intervention. In Hungary for example, one of the countries with the highest suicide rates in the world, a significant decrease in the numbers of suicidal attempts and suicides was achieved recently owing to a very intensive campaign to prevent depression (Rihmer and Kiss, 2002; Rihmer et al. 2001).

In the complex approach to fight off depression and its serious consequences drugs play a leading role. Drug therapy in depression is for the time being based on the firm knowledge that mood can be efficiently influenced via the mesencephalic catecholaminergic and serotonergic systems in the brain. The many times verified clinical experience that drugs depleting noradrenaline are lowering mood, those that increase the availability of noradrenaline increase it, substantially supports the original hypothesis of Schildkraut (1965) that catecholamine deficiency in the brain leads to depression. Extensive studies showed later that brain serotonin plays a similar role in the etiology of depression (Caldecott-Hazard et al. 1991). This is proved by the high therapeutic efficiency of the selective serotonin reuptake inhibitors (SSRIs) (Mace and Taylor, 2000). Also dopamine deficiency in depression and increased dopaminergic activity in mania was demonstrated (Stahl, 2000).

Although efficient drugs are already available there is still a great need for further development in drug therapy of major depression. In this context it is reasonable to focus attention on a rapidly developing new line of research based on the recent discovery of the enhancer regulation in the mesencephalon (see Knoll, 2003 for review). A remarkable step in this research was the demonstration that well-known trace amines in the brain, \(-\)phenylethylamine (PEA) and tryptamine are endogenous mesencephalic enhancer substances (Knoll et al. 1996b). A further step was the proof that \(-\)-deprenyl (Selegiline), a drug well-known since decades as a selective inhibitor of B-type monoamine oxidase (MAO), used now worldwide in Parkinson’s disease and more recently in Alzheimer’s disease, is a PEA-derived synthetic mesencephalic enhancer substance (Knoll et al., 1996a). The next, from therapeutic aspects probably the most promising step, was the development of \(-\)-1-(benzofuran-2-yl)-2-propylaminopentane, \(-\)-BPAP, the first tryptamine-derived selective and highly potent synthetic mesencephalic enhancer substance that opens a previously unknown possibility to keep the activity of the noradrenergic, dopaminergic and serotonergic neurons in the brain on a higher activity level (Knoll et al. 1999).

The aim of this review is a brief survey of the current drug therapy of depression, an overview of the state of the art in enhancer research as a new promise to enlarge our armamentary to fight off depression, and the discussion of the prospects to significantly decrease by means of enhancer substances the number of therapy resistant cases.

MAJOR DEPRESSION AND BIPOLAR DISORDERS

According to the revision of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) a major depressive disorder (unipolar depression) occurs without a history of manic or hypomanic episode.

Major depressive disorder is a common one, with 15% life-time prevalence (about 25% for women). Biological, genetic and psychosocial factors play a role in the etiology of major depression and bipolar disorders. Regarding the biological factors the overwhelming majority of the papers claim the relation of noradrenaline, serotonin, and dopamine to depression, but we find hints to a role of GABA and other neurotransmitters, as well as to changes in hormonal secretion (cortisol, thyroid and/or growth hormone), or to alterations of Substance P and neurokinin receptor 1, etc.

According to Stahl (2000) depression modifies neurotransmission in the brain by at least the following mechanisms: (1) modification of molecular neurobiology; (2) loss of neuronal plasticity; (3) excitotoxicity; (4) absence of neurotransmission; (5) excess of neurotransmission; (6) an imbalance among neurotransmitters; (7) the wrong rate of neurotransmission; (8) the wrong neuronal wiring.
THE CURRENTLY USED ANTIDEPRESSANTS AND THEIR EFFECT ON NEUROTRANSMISSION

Monoamine oxidase inhibitors (MAOIs). MAOIs are antidepressants because they block the breakdown of catecholamines and serotonin and facilitate thereby neurotransmission. As the imminent reuptake of catecholamines and serotonin released in response to stimulation is the main mechanism that eliminates the transmitter from the extraneuronal space, MAOIs are necessarily much less effective as antidepressant agents than uptake inhibitors. Nevertheless, serious side-effects (cheese-effect) restricted their clinical use much before the introduction of the uptake inhibitors. Their use in the therapy of depression is modest.

The tricyclic and tetracyclic antidepressants (TCAs). TCAs block the reuptake of noradrenaline and serotonin. They are also competitive antagonists at the muscarinic acetylcholine, histamine H₁, and 1- and 2-adrenergic receptors. The major therapeutic effect of the TCAs are due to their effect on noradrenergic and serotonergic transmission in the central nervous system. The anticholinergic property, however, produces adverse effects mediated by the autonomic nervous system. TCAs are effective in a wide range of disorders, first of all in major depression.

Selective serotonin reuptake inhibitors (SSRIs). Drugs belonging to this group – fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram – are today the first-line agents for treatment of depression and related disorders. They have relatively little effect on the reuptake of noradrenaline and almost no effect on the reuptake of dopamine. Due to their selectivity they possess a more advantageous adverse events profile than TCAs. SSRIs can be combined with other antidepressants.

Other antidepressants. Reboxetine used as a prototype of the selective noradrenergic reuptake inhibitors (NRIs) blocks preferentially noradrenaline reuptake with a little effect on serotonin reuptake. Venlafaxine a selective serotonin and noradrenergic reuptake inhibitor (SNRI) is at present the only dual-action antidepressant in use. Mirtazepine acts in depression by increasing synaptic levels of noradrenaline and serotonin as an antagonist of the presynaptic 2-adrenergic receptors in the brain. None of them improved significantly antidepressant drug therapy.

THE MESENCEPHALIC ENHANCER REGULATION. NATURAL AND SYNTHETIC MESENCEPHALIC ENHANCER SUBSTANCES

The role of (-)-deprenyl in the recognition of the enhancer regulation in the mesencephalic neurons. A 30-year lasting thorough analysis of the mechanism of action of (-)-deprenyl resulted finally in the recognition of the enhancer regulation in the mesencephalic catecholaminergic neurons (Knoll, 1998). The history how this crucially important physiological mechanism remained undetected for decades gives a good instance of concealed traps in research.

Knoll developed (-)-deprenyl in the early 60s (see Knoll, 1983 for reviewing the early history of its development). When he started to develop (-)-deprenyl MAO inhibitors were in the center of interest. Both as experimental tools and as therapeutic agents MAO inhibitors have exercised an important influence on the development of the widely accepted hypothesis that depression is associated with diminished monoaminergic tone in the brain and that depressed patients treated with antidepressants become elated because of enhanced biological activity of monoamine transmitters in the central nervous system.

Deprenyl (first described with the code name E-250) was selected for development because of its unique pharmacological profile. In contrast to MAO inhibitors it did not potentiate the blood pressure increasing effect of amphetamine, the releaser of noradrenaline from the intraneuronal stores, but inhibited it. This was described in the first paper of deprenyl (see Fig. 1 in Knoll et al., 1965). Since Blackwell discovered in 1963 that MAOIs inhibit the breakdown of tyramine and this is the cause of the sometimes fatal hypertensive crisis in patients on MAOI who ate to much cheese rich in tyramine (cheese-effect), the development of MAOI without the cheese effect was of high promise.

Further studies revealed that (-)-deprenyl is a unique MAO inhibitor, the only one that does not potentiate the effect of tyramine but inhibits it. This was first shown in a study performed on cats and on the isolated vas deferens of rats. The authors expressed their hope that this tyramine inhibiting property of the compound may be valuable for human therapy (Knoll et al. 1968).
In the same year when they arrived at this conclusion with (-)-deprenyl, a substance, later named clorgyline, was described that came into world-wide use as an experimental tool in MAO research (Johnston, 1968). Johnston realized that his substance preferentially inhibits the deamination of serotonin, and proposed the existence of two forms of MAO, one highly sensitive to clorgyline and one relatively insensitive to it. He introduced the terms “type A” and “type B” MAO, MAO-A being selectively inhibited by clorgyline. This nomenclature has become widely accepted and is still in use.

Knoll discovered in 1970 that (-)-deprenyl was the missing link. This was proved and (-)-deprenyl was described as the first highly selective inhibitor of MAO-B (Knoll and Magyar, 1972). For several years the selective MAO-B inhibitory effect was at the center of interest and delayed the discovery of the drug’s enhancer effect. It was the MAO inhibitory effect of the compound that led to the first clinical application of (-)-deprenyl.

Later sexual activity of male rats was selected as a quantitatively measurable rapidly aging dopaminergic function to compare the effect of (-)-deprenyl versus saline treatment on the age-related decline of the mesencephalic dopaminergic machinery (Knoll, 1982). (-)-Deprenyl treatment significantly slowed the age-related decay of sexual performance and this effect was unrelated to the inhibition of MAO-B. This was shown with the development of (-)-1-phenyl-2-propylaminopentane, (-)-PPAP. This derivative of (-)-deprenyl that was intentionally developed to share the pharmacological profile with (-)-deprenyl but being free of MAO-B inhibitory property (Knoll et al., 1992). (-)-PPAP enhanced dopaminergic activity in the brain like (-)-deprenyl. Knoll’s progress in clarifying the mechanism of action of (-)-deprenyl responsible for enhanced dopaminergic activity can be followed in his sequent reviews (Knoll, 1978, 1983, 1987, 1992, 1995), until he came to the final conclusion that (-)-deprenyl acts primarily as a PEA-derived synthetic mesencephalic enhancer substance (Knoll, 1998).

Since (-)-PPAP, like (-)-deprenyl, inhibited on isolated smooth muscle tests the uptake of tyramine, Knoll first believed that this effect is responsible for the enhanced dopaminergic activity following the administration of these compounds. Further studies revealed, however, that (-)-PPAP, like its parent compound, (-)-deprenyl, is a PEA-derived synthetic enhancer substance (Knoll, 1998).

The thorough analysis of the dose-dependent effect of (-)-deprenyl on the release of catecholamines and serotonin in physiological quantities by the aid of HPLC 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) revealed the existence of the enhancer regulation in the mesencephalic neurons. Knoll and Miklya treated rats with 0.01, 0.025, 0.05, 0.1 and 0.25 mg/kg (-)-deprenyl, respectively, once daily for 21 days, isolated the discrete rat brain regions 24 hours after the last injection and measured the biogenic amines released during 20 min from the freshly isolated tissue samples. The amount of dopamine released from the substantia nigra and tuberculum olfactorium clarified that the dopaminergic neurons worked on a significantly enhanced activity level even in the brain of rats treated with the lowest, 0.01 mg/kg dose of (-)-deprenyl. As this small dose of (-)-deprenyl leaves the MAO-B activity and the uptake of amines practically unchanged, this study was the first unequivocal demonstration for the operation of a hitherto unknown enhancer mechanism in the dopaminergic neurons that is stimulated by (-)-deprenyl in very low doses (Knoll and Miklya, 1994).

Further studies clarified the operation of the mesencephalic enhancer regulation and allowed to realize that PEA, the parent compound of (-)-deprenyl is primarily an endogenous enhancer substance, and exerts in higher concentrations its well known effect, the release of catecholamines from their intraneuronal stores. It became clear that this effect covered up completely the enhancer effect and prevented its detection, thus PEA was classified as the prototype of the indirectly acting sympathomimetics. Amphetamine and methamphetamine, PEA-derivatives with a long lasting effect, share with their parent compound the releasing property. (-)-Deprenyl was the first PEA/methamphetamine-derivative that maintained the enhancer effect of its parent compounds but lost completely the releasing property. This peculiar change in the pharmacological spectrum of this PEA-derivative enabled finally to discover the enhancer regulation as this effect was not covered up by the release of catecholamines from their intraneuronal stores (Knoll and Miklya, 1995; Knoll et al., 1996a,b,c; see for review Knoll, 1998, 2001, 2003).

In the light of Knoll’s studies there is no doubt that clinicians were mistaken from the very begin-
ning who used (-)-deprenyl in the belief that the therapeutic benefits observed in patients treated with this drug was due to the selective inhibition of MAO-B in the brain. The overwhelming majority of the clinical benefits was due to the enhancer effect of (-)-deprenyl (Knoll, 1998).

The essence of the mesencephalic enhancer regulation. PEA and tryptamine, endogenous mesencephalic enhancer substances. The enhancer regulation is defined as: the existence of enhancer-sensitive neurons in the brain capable of working in a split second on a significantly higher activity level due to endogenous enhancer substances of which, for the time being, only PEA and tryptamine are the experimentally analyzed examples (Knoll, 2001, 2003).

The catecholaminergic and serotonergic neurons in the mesencephalon are excellent models to study the enhancer regulation as their physiologic function is to supply continuously the brain with proper amounts of catecholamines and serotonin that influence – activate or inhibit – billions of neurons. The significant enhancement of the nerve-stimulation induced release of $[^3H]$-noradrenaline, $[^3H]$-dopamine, and $[^3H]$-serotonin from the isolated brain stem of the rat in the presence of PEA (Fig. 1) or tryptamine (Fig. 2) is shown to illustrate the enhancer regulation in function.

From a freshly isolated brain stem of a properly pretreated rat a stable amount of the labelled transmitters is released for a couple of hours (Knoll and Miklya, 1995). Electrical stimulation of the brain stem significantly increases the outflow of the transmitters. The calculated average amount of each of the labelled transmitters released from the stimulated brain stem is the product of a surviving population of specific neurons with large individual variation in their performance. Neurons respond to stimulation in an “all or none” manner. Hence, prior to the administration of PEA or tryptamine, only the high performing members of the population respond with transmitter release to electrical stimulation. As PEA or tryptamine enhance specifically the excitability of the enhancer-sensitive neurons, the stimulation-evoked release of the labelled transmitter changed accordingly.

The data in Fig. 1 and 2 show a remarkable quantitative difference between PEA and tryptamine in their effectiveness on serotonergic neurons. A lower concentration of tryptamine (1.3 µmol/l) proved to be much more potent than a

**Fig. 1.** The significant enhancement of the nerve stimulation induced release of $[^3H]$-noradrenaline, $[^3H]$-dopamine, and $[^3H]$-serotonin, respectively, from the isolated brain stem of the rat in the presence of -phenylethylamine (PEA). (N=8).
much higher concentration of PEA (16 µmol/l) in enhancing the stimulation-evoked release of serotonin. This indicates that the enhancer regulation in the catecholaminergic and serotonergic neurons are not identical on the molecular level.

According to Knoll the existence of an enhancer regulation brings different perspective to the brain-organized goal-oriented behavior since enhancer-sensitive neurons are always ready to increase immediately their activity in response to endogenous enhancer substances and represent the device in the mammalian brain that operates in fact as the *vis vitalis*. Any act in the endless “fight for existence” drama in nature illustrates the crucial importance of the enhancer regulation for survival. “When the eagle pounces upon its chosen victim with lightning speed, and both the attacker and the potential victim have only a split second to become properly activated, the chance for the eagle to obtain its food and for the victim to save its life lies in the mechanism that specific endogenous enhancer substances dynamically increase the performance of the proper enhancer-sensitive neurons according to the need and the partner with the more efficiently activated brain will reach its goal” (see Knoll 1994, 2003 for review).

The recent realization of the enhancer regulation in the brain is obviously the very beginning of a new line of research. PEA and tryptamine, the first examples of physiologic enhancer substances represent the peak of an iceberg. The development of a tryptamine-derived synthetic enhancer substance that increased the performance of cultured hippocampal neurons with a peak effect at 10^{-14} M concentration (see Knoll et al., 1999, Fig. 5) foreshadows the existence of much more potent physiologic enhancer substances in the mesencephalon than PEA and tryptamine and incites research in this direction.

**(-)-DEPRENYL AND (-)-BPAP, PROTOTYPES OF SYNTHETIC MESENCEPHALIC ENHANCER SUBSTANCES**

(-)-Deprenyl, the PEA-derived representative synthetic mesencephalic enhancer substance. (-)-Deprenyl, developed in the early 1960s as a new spectrum psychostimulant and potent MAO inhibitor, proved to be later, as the first selective inhibitor of MAO-B, indispensable for investigating the nature and function of B-type MAO. Hundreds of clinical studies with the drug were designed thereafter in the firm belief that selective blockade of MAO-B was responsible for all the effects that followed (-)-deprenyl medication. Realizing that PEA, known to be a releaser of catecholamines, is an endogenous enhancer substance and (-)-deprenyl is a PEA-derived synthetic enhancer substance devoid of the catecholamine releasing property of its parent compound, clarified that, as a matter of fact, the enhancer effect of (-)-deprenyl was re-
sponsible for the majority of the beneficial effects of the drug described in various experimental and clinical studies (Knoll, 1998, 2001).

Being rapidly metabolized by MAO, PEA is short acting, and its enhancer effect can be detected in in vitro experiments only. As (-)-deprenyl is not metabolized by MAO, its effect is long lasting and it can reliably be measured in vivo in a dose-dependent manner. The most convenient method for in vivo testing of the enhancer effect of a compound is to measure the release of catecholamines and serotonin from discrete brain areas by the aid of HPLC with electrochemical detection. Knoll and Miklya measured the release of noradrenaline from the locus coeruleus, dopamine from the striatum, substantia nigra and tuberculum olfactorium and serotonin from the raphe isolated from rats pretreated with the enhancer substance (Knoll and Miklya, 1995). The subcutaneous administration of (-)-deprenyl enhanced the activity of the catecholaminergic neurons in a dose-dependent manner. This effect was shown on the noradrenergic and dopaminergic neurons. (-)-Deprenyl treatment, however, did not enhance the activity of the serotonergic neurons. (-)-Deprenyl is a PEA-derived enhancer substance and its in vivo ineffectiveness on serotonergic neurons is in harmony with the finding that in the in vitro experiments too PEA was much less potent than tryptamine in enhancing the activity of the serotonergic neurons when the endogenous enhancer substances were given into the organ bath of isolated discrete brain areas (compare Fig. 1 to Fig. 2).

Since (-)-deprenyl is a highly potent and selective inhibitor of MAO-B, a structure-activity-relationship study was performed to develop a deprenyl-derived enhancer substance being free of the MAO-B inhibitory property (Knoll et al., 1992), and (-)-PPAP is at present the reference substance with this pharmacological profile.

(-)-BPAP. The tryptamine-derived representative synthetic mesencephalic enhancer substance. The discovery that tryptamine is also an endogenous enhancer substance (Knoll, 1994) opened the way for the synthesis of a new family of enhancer compounds unrelated to PEA and the amphetamines. (-)-BPAP was selected as the reference compound for further studies (Knoll et al., 1999). For details of its chemistry see: Oka et al., 2001, Yoneda et al., 2001.

The in vivo dose-dependent enhancer effect of (-)-BPAP on noradrenergic, dopaminergic, and serotonergic neurons proved that this compound showed a substantially higher potency than (-)-deprenyl. (-)-BPAP, the highly selective tryptamine-derived synthetic mesencephalic enhancer substance is for the time being the best experimental tool for the analysis of the mesencephalic enhancer regulation.

(-)-BPAP significantly enhanced in 0.18 nmol concentration the impulse propagation mediated release of [3H]-noradrenaline and [3H]-dopamine and in 36 pmol concentration the release of [3H]-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. Racemic BPAP protected cultured hippocampal neurons from the neurotoxic effect of amyloid$_{25-35}$ fragment in $10^{14}$ M concentration. In rats (-)-BPAP significantly enhanced the activity of the catecholaminergic and serotonergic neurons in the brain 30 min 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 (Knoll et al. 1999).

In a recent study the effect of (-)-BPAP was compared to that of the known stimulants of catecholaminergic and/or serotonergic neurons (desmethylimipramine, fluoxetine, clorgyline, lazabemide, pergolide, bromocriptine) on electrical stimulation induced release of the labelled transmitters from the isolated brain stem of rats following the incorporation of [3H]-noradrenaline or [3H]-dopamine or [3H]-serotonin by preincubation into the transmitter stores. 50 ng/ml (-)-BPAP was the most effective concentration in enhancing the nerve stimulation induced release of [3H]-noradrenaline and [3H]-dopamine, 10 ng/ml (-)-BPAP was highly effective in enhancing the release of [3H]-serotonin. In contrast, 250 ng/ml desmethyliimipramine (DMI), a selective inhibitor of the uptake of noradrenaline, did not change significantly the nerve stimulation induced release of [3H]-noradrenaline and 50 ng/ml fluoxetine, a selective inhibitor of the uptake of serotonin, did not change the release of [3H]-serotonin. Neither 250 ng/ml clorgyline, a selective inhibitor of MAO-A, nor 250 ng/ml lazabemide, a selective inhibitor MAO-B, was capable to significantly increase the nerve stimulation induced release of either [3H]-serotonin or [3H]-noradrenaline. The potent dopamine receptor agonists, pergolide and bromocrip-
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Thus the results proved that stimulation of catecholaminergic and serotonergic neurons in the brain via the enhancing mechanism is clearly different from influencing uptake or MAO (Miklya and Knoll, 2003).

The subcutaneous administration of 1 mg/kg tetrabenazine, once daily for 5 days, which depletes the catecholamine stores in the brain, significantly inhibits in rats the acquisition of a two-way conditioned avoidance reflex in the shuttle box. Enhancer substances, antagonize in a dose-dependent manner the inhibition of learning caused by tetrabenazine. The tryptamine-derived selective and highly potent enhancer, (-)-BPAP acted in dose range from 0.05 to 10 mg/kg. The PEA-derived enhancer substances, (-)-deprenyl and (-)-PPAP were much less active (1-5 mg/kg). 1-(Benzofuran-2-yl)-2-(3,3,3-trifluoropropyl)-am inopentane HCl [3-F-BPAP], a newly synthetized analogue of (-)-BPAP with low specific activity, significantly antagonized the enhancer effect of (-)-BPAP but left the effect of (-)-deprenyl and (-)-PPAP unchanged. This was the first proof for a difference in the mechanism of action between a PEA-derived enhancer substance and its tryptamine-derived peer (Knoll et al., 2002a).

(-)-BPAP, enhanced the performance of midbrain neurons, both in vivo and ex vivo, in a characteristic bi-modal manner, presenting one bell shape dose/concentration effect curve in the low nanomolar range and another at higher micromolar range. For example, 4.7±0.10 nmol/g wet weight noradrenaline was released within 20 min from the quickly removed locus coeruleus of saline treated rats. This amount was increased 30 min after the subcutaneous administration of 0.0005 mg/kg (-)-BPAP to 15.4±0.55 nmol/g (p<0.001). However, the injection of a hundred times higher, 0.05 mg/kg dose of (-)-BPAP, the amount of noradrenaline (4.3±0.25 nmol/g) released from the locus coeruleus did not differ from the control value. In ex vivo experiments, when the isolated locus coeruleus was soaked in an organ bath containing (-)-BPAP, the release of noradrenaline was significantly enhanced from 10^{-16} M concentration, reached a peak effect at 10^{-13} M concentration, but 10^{-10} M (-)-BPAP was ineffective. A significant enhancer effect was detected also in the high concentration range from 10^{-6} M, the peak effect was reached at 10^{-6} M concentration and 10^{-5} M (-)-BPAP was ineffective. (-)-BPAP enhanced in the low concentration range the performance of dopaminergic and serotoninergic neurons with a peak effect at 10^{-13} and 10^{-12} M concentration, respectively (Knoll et al. 2002b). The authors concluded that (i) high and low affinity „enhancer“ receptors exist in the brain, and (ii) that they may be identified with the recently cloned family of the “trace amine” receptors, activated by PEA and tryptamine, the prototypes of the endogenous enhancer substances (Borowsky et al., 2001).

THE RATIONALE TO ENLARGE OUR ARMAMENTARY TO FIGHT OFF DEPRESSION WITH THE INTRODUCTION OF SYNTHETIC MESENCEPHALIC ENHANCER SUBSTANCES

Considering the unequivocal experimental and clinical evidence that catecholamines and serotonin in the brain play a crucial role in the control of mood, and major depression is due primarily to a deficiency in the activity of these systems, the antidepressant effect of enhancer substances is self explanatory. Up to the present, (-)-deprenyl is the only synthetic mesencephalic enhancer substance that was widely used in the clinic. The drug was primarily used in Parkinson”s disease. This illness is very often accompanied by depression. Youdim (1980), Miyoshi (2001), Zesiewicz et al. (1999), Tom and Cummings (1998) treated Parkinson”s disease with (-)-deprenyl and realized the antidepressant effect of the drug.

(-)-Deprenyl was found to be an antidepressant. This effect was originally demonstrated by Varga (1965) and Varga and Tringer (1967) with the racemic compound and in 1971 with the (-)-enantioomer (Tringer et al., 1971). The first study that corroborated the antidepressant effect of (-)-deprenyl was published by Mann and Gershon (1980).

The realization of the peculiar effect of (-)-deprenyl, first in Parkinson's disease and later in Alzheimer's disease, distracted attention from its antidepressant property which remained unutilized. Even an especially interesting aspect of this problem fell into oblivion. In a study performed by Birkmayer et al. (1984) on 102 outpatients and 53 inpatients (-)-deprenyl was given together with (-)-phenylalanine, the precursor of PEA that in contrast to PEA crosses the blood-brain barrier and being metabolized in the brain increases the concentration of this endogenous enhancer substance. Nearly 70% of the patients achieved full...
remission. The outstanding clinical efficiency equaled only that of electroconvulsive treatments (ECT), but without the memory-loss side effect of ECT.

Quintin et al. (1984) found (-)-deprenyl effective against atypical depression. This open trial on 17 patients made the finding questionable. But McGrath et al. (1989) in a placebo-controlled trial of (-)-deprenyl proved the efficiency of the drug in atypical depression. In a double blind evaluation Mendlewicz and Youdim (1983) found (-)-deprenyl treatment successful in major depression. Some authors (Ritter and Alexander, 1997; Kuhn and Muller, 1996; Lees, 1991) realized marked antidepressant effect of high doses of (-)-deprenyl (40-60 mg/day). In a study of Bodkin and Amsterdam (2002) the transdermal application of (-)-deprenyl was effective in double-blind, placebo controlled parallel groups examinations in outpatients. Amsterdam (2003) controlled the trial and found a good antidepressant effect of (-)-deprenyl.

Unfortunately, (-)-deprenyl was nowhere registered as an antidepressant agent. Considering the pharmacology of (-)-deprenyl there is good reason to accept the conclusion that the enhancer effect of the compound is responsible for the observed antidepressant efficacy of the drug (Knoll, 1998).

(-)-BPAP is about 130 times more potent than (-)-deprenyl in rats for antagonizing tetrabenzine-induced depression in the shuttle box. As was discussed previously, (-)-BPAP, in contrast to (-)-deprenyl, is a highly efficient enhancer of the serotonergic neurons in the mesencephalon. In all the experimental studies performed with (-)-BPAP in comparison to (-)-deprenyl, the tryptamine-derived enhancer substance proved to be substantially more potent than the PEA-derived compound. There is good reason to expect that (-)-BPAP will surpass the antidepressant effect of (-)-deprenyl.

The fact that the presently used selective uptake inhibitors and the enhancer substances stimulate the catecholaminergic and serotonergic neurons in the brain via quite different mechanisms make reasonable to use in the future representatives of this two groups of compounds simultaneously in depressed patients. With the proper combination of (-)-BPAP and a selective uptake inhibitor we may in the future achieve a significantly better final result as with one type of these drugs. The possibility to fight off depression with this combination in a higher percentage of patients would be of high practical importance as a considerable percentage of persons suffering in major depression cannot be cured with the available antidepressants.

(-)-Deprenyl, the only synthetic mesencephalic enhancer substance in clinical use is known to be a safe, well-tolerated drug. (-)-BPAP, which is as an enhancer substance at least 100-times more potent than (-)-deprenyl, is better tolerated than (-)-deprenyl. Even several 100-times higher doses of (-)-BPAP than the ones that exert an enhancer effect can be administered without risk of detectable side-effects. It seems therefore reasonable to expect that the addition of (-)-BPAP to the armamentary of antidepressants may substantially decrease the number of therapy resistant cases.

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