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Review

Enhancer Regulation/Endogenous and Synthetic Enhancer Compounds: A Neurochemical Concept of the Innate and Acquired Drives

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This review is to summarize experimental evidence and theoretical consideration in support of the concept that a mesencephalic enhancer regulation is the basis of the limited number of innate drives indispensable for the survival of the individual and the species, while a specifically organized telencephalic enhancer regulation is the basis of the acquired drives to reach an unlimited number of dispensable goals. The study is also an overview of the experimental and clinical data supporting the proposal that, due to the progressive decay of the mesencephalic enhancer regulation with the passing of time, the prophylactic administration of a synthetic enhancer substance [(−)-deprenyl, (−)-BPAP] during postdevelopmental life could significantly slow the age-related decay of behavioral performances, prolong life, and prevent the precipitation or delay the onset of Parkinson's disease and Alzheimer's disease.

KEY WORDS: Innate drives; acquired drives; enhancer regulation; enhancer substances; (−)-deprenyl (Selegiline); *R*-(−)-1-(benzofuran-2-yl)-2-propylaminopentane [(−)-BPAP]; antiaging drugs; depression; Parkinson's disease; Alzheimer's disease.

INTRODUCTION

In behavioral studies, *drive* is the commonly used technical term to define the force that activates the mammalian organism, the inner urge that stimulates a response, inciting activity, a basic or instinctive need, such as hunger drive, sexual drive, and so on.

The neurochemical basis of both categories of drives, that of the innate ones to reach the limited number of indispensable goals needed for the survival of the individual and the species, and that of the acquired drives to reach an unlimited number of dispensable goals, is unknown. The mesencephalic mechanism that keeps the innate drives in action is the presumably less complicated part of the problem. The real hard nut to crack seems to be the cortical mechanism that renders the acquisition of an "unnatural" urge possible.

Being familiar with a technical term, we may occasionally have the fallacious impression of possessing full knowledge of the subject it connotes. For example, if an eagle attempts to catch a rabbit, the rabbit has a split second to react. Common sense, the practical judgement that is independent of specialized knowledge, has a simple and convincing interpretation. Hunger drives the eagle and fear drives the rabbit. In reality, "drive" is just a useful description for the still unknown brain mechanism that activates the organism and keeps it going on until the goal is reached.

Based (i) on previous efforts to reveal the mechanism of the innate and acquired drives (see 1,2 for review) and (ii) recent developments in the field (see 3 for review), this study is an attempt to translate "drive" into the language of neurochemistry.

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For living beings with highly refined organization, the telencephalon has absolute priority in maintaining the sophisticated integration among an apparently confusing network of cells, synchronizing them to a lucidly arranged, harmoniously operating, ultrastable system. For a highly refined organism, "life" means the operation of the integrative work of the brain, and "natural death" means the blacking out of this function. This is clearly shown by the fact that cells of vital organs, including the brain, maintain vigorous activity at natural death.

Mesencephalic enhancer regulation, primarily its operation in the catecholaminergic neurons, keeps the telencephalon active and thus the system alive. The operation of the catecholaminergic system is comparable to an engine ignited once and for all in an early phase of development, signaled by the appearence of the (EEG) electroencephalographic activity. By its enhancer regulation, the catecholaminergic system is dynamically changing the activation of the telencephalon during lifetime according to need. Life is terminated because of the progressive decay of the efficiency of the catecholaminergic system during postdevelopmental life span, until at some point, in an emergency situation, the integration of the parts in a highly sophisticated entity can no longer be maintained and natural death, signaled by the disappearence of EEG activity, sets in.

The catecholaminergic tone is determinant for the three basic modes of brain activity. The system performs at its lowest possible level in the nonvigilant resting state (sleeping); performs at a steady low level in the vigilant resting state (leisure); and operates, according to need, at a dynamically enhanced activity level in the active state (assault/escape behavior, goal-seeking).

With the development of the human brain, a network with about 300 billion interrelated nerve cells and 10^{10}-bit capacity, the matter from which the conscious psychic experience is inseparable, living organisms reached on earth their highest level of organization. The psychic experience, the most miraculous product of nature, though inseparable from the measurable changes in the neurons, is obviously not a simple product of these changes. The objective and subjective aspects of brain activity, interrelated as the outside and the inside of the same thing, make that in its integrity the operation of the brain is both within and beyond the realm of natural sciences. The ancient philosophical question whether "The Self and Its Brain" (4) or "The Brain and its Self" is the correct approach, does not bear on the objectively analyzable, cognizable nature of the unknown neurochemistry of the drives.

This review sums up experimental evidence and theoretical consideration in support of the concept that an until recently unknown brain mechanism, the enhancer regulation in the mesencephalic neurons, is responsible for the innate drives and a special form of it in the telencephalon for the acquired ones. Furthermore, it will be argued that age-related changes in the enhancer regulation of the catecholaminergic brain engine are primarily responsible for (i) the youthful power of the mammals from weaning until sexual maturity, (ii) the transition from the uphill period of life into postdevelopmental longevity, (iii) the progressive decay of behavioral performances during the downhill period, and (iv) the transition from life to death. The practical objective of this review is to reinforce the concept (3) that prophylactic administration of a synthetic enhancer substance during postdevelopmental life could significantly slow the age-related decay of behavioral performances, prolong life, and prevent the precipitation or delay the onset of Parkinson's disease and Alzheimer's disease.

OVERVIEW OF THE ENHANCER REGULATION: NATURAL AND SYNTHETIC ENHANCER SUBSTANCES

The Essence of the Enhancer Regulation. β-Phenylethylamine (PEA) and Tryptamine, Endogenous Enhancer Substances

We can define the enhancer regulation as the existence of enhancer-sensitive neurons in the brain capable of working in a split second on a significantly higher activity level because of endogenous enhancer substances of which, for the time being, only β-phenylethylamine (PEA) and tryptamine are the experimentally analyzed examples (see 3 for review).

The catecholaminergic and serotonergic neurons in the mesencephalon are the best models to study the enhancer regulation because their physiological function is to continuously supply 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 [^{3}H]-norepinephrine, [^{3}H]-dopamine, and [^{3}H]-serotonin from the isolated brain stem of the rat in the presence of PEA (Fig. 1) or tryptamine (Fig. 2) illustrates the enhancer regulation in function.

From a freshly isolated brain stem of a properly pretreated rat a stable amount of the labeled transmitters is released for a couple of hours (see 7 for methodology). Electrical stimulation of the brain stem

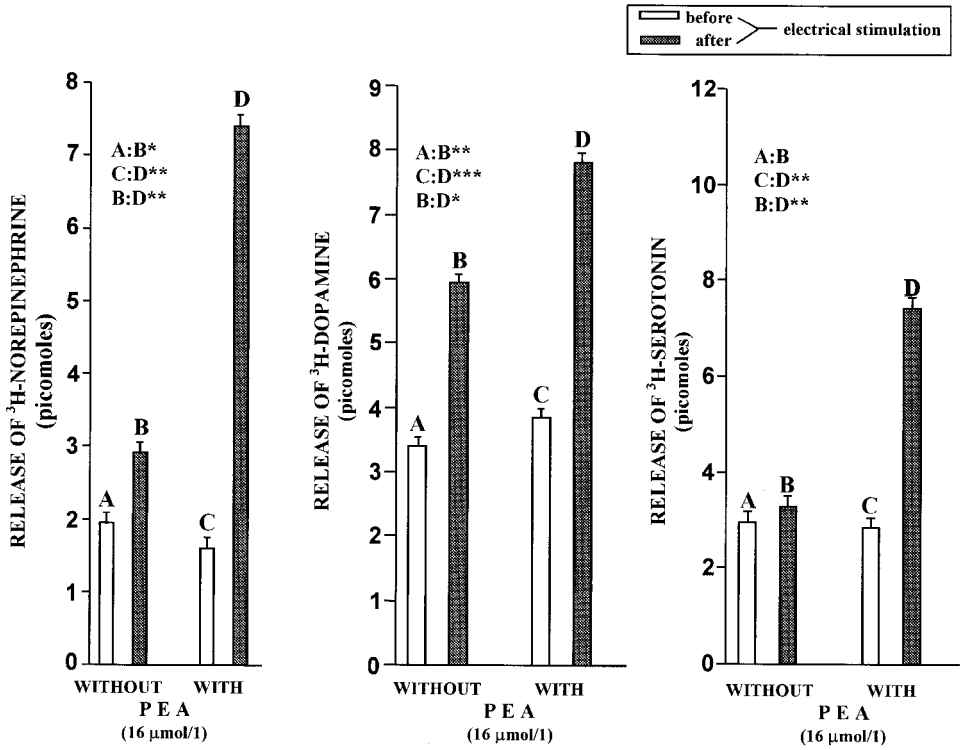

Fig. 1. The significant enhancement of the nerve stimulation induced release of [^{3}H]-norepinephrine, [^{3}H]-dopamine, and [^{3}H]-serotonin, respectively, from the isolated brain stem of the rat in the presence of β-phenylethylamine (PEA) (n = 8). Each column represents the amount of the labeled transmitter in picomoles released in a 3-min collection period. See 7 for methodology. Vertical lines show SEM. Paired Student's t test. $*P < .05$, $**P < .01$, $***P < .001$.

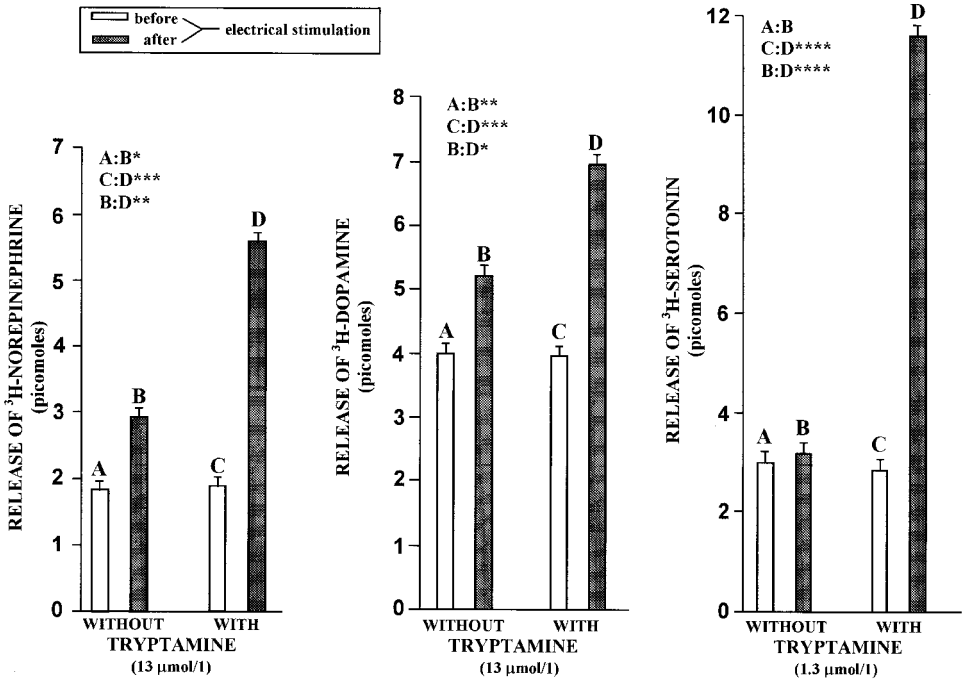

Fig. 2. The significant enhancement of the nerve stimulation induced release of [^{3}H]-norepinephrine, [^{3}H-dopamine, and [^{3}H]-serotonin, respectively, from the isolated brain stem of the rat in the presence of tryptamine (n = 8). Each column represents the amount of the labeled transmitter in picomoles released in a 3-min collection period. See 7 for methodology. Vertical lines show SEM. Paired Student's t test. $*P < .05$, $**P < .02$, $***P < .01$, $****P < .001$.

significantly increases the outflow of the transmitters. The calculated average amount of each of the labeled 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, before the administration of PEA or tryptamine, only the high-performing members of the population responded with transmitter release to electrical stimulation. PEA or tryptamine enhance specifically the performance of the enhancer-sensitive neurons, and the stimulation-evoked release of the labeled transmitter changed accordingly.

The data in Figs. 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 much higher concentration of PEA (16 μmol/L) in enhancing the stimulation-evoked release of serotonin. This by itself is a broad hint to the multiplicity of the enhancer receptors related to the mesencephalic enhancer regulation.

The existence of an enhancer regulation brings different perspective to brain-organized goal-oriented behavior because 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 *de facto* 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 on its victim, the victim's reaction is a matter of life and death. 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 of the specific endogenous enhancer substances that dynamically increase the performance of the proper enhancer-sensitive neurons according to the need, and the animal with the more efficiently activated brain will reach its goal (1–3).

The recent realization of the activity of enhancer regulation in the brain is the beginning of a new line of research. PEA and tryptamine, the first examples of physiological enhancer substances represent the peak of an iceberg. The development of a tryptamine-derived synthetic enhancer substance that increases the performance of cultured hippocampal neurons with a peak effect at 10^{-14} M concentration (see 12, Fig. 5) foreshadows the existence of much more potent physiological enhancer substances in the mesencephalon than PEA and tryptamine and incites research in this direction.

(−)-Deprenyl (Selegiline) and *R*-(−)-1-(Benzofuran-2-yl)-2-Propylaminopentane [(−)-BPAP], Prototypes of Synthetic Enhancer Substances

(−)-Deprenyl: The PEA-Derived Representative Synthetic Enhancer Substance. (−)-Deprenyl (selegiline), developed in the early 1960s as a new-spectrum psychostimulant and potent monoamine oxidase inhibitor (MAOI) (5), proved to be later, as the first selective inhibitor of MAO-B (6), 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 (7) and (−)-deprenyl is a PEA-derived synthetic enhancer substance devoid of the catecholamine releasing property of its parent compound (8), clarified that the enhancer effect of (−)-deprenyl was responsible for the majority of the beneficial effects of the drug described in various experimental and clinical studies (see 3 and 9 for review).

Being rapidly metabolized by MAO, PEA is short acting, and its enhancer effect can be detected in *in vitro* experiments only (Figs. 1 and 2). Because (−)-deprenyl is not metabolized, 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. We measured the release of norepinephrine 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 (see 10 for details of methodology).

The subcutaneous administration of (−)-deprenyl enhanced the activity of the catecholaminergic neurons in a dose-dependent manner. This effect is shown on noradrenergic neurons (Fig. 3) and dopaminergic neurons (Fig. 4). (−)-Deprenyl treatment, however, did not enhance the activity of the serotonergic neurons (Fig. 5). (−)-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 PEA was much less potent than tryptamine in enhancing the activity of the serotonergic neurons (compare Fig. 1 to Fig. 2).

Because (−)-deprenyl is a highly potent and selective inhibitor of MAO-B, we performed a structure–activity relationship study to develop a deprenyl-derived

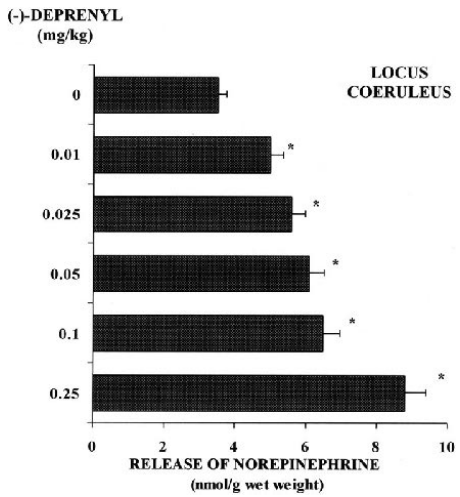

Fig. 3. The significant enhancement of the release of norepinephrine from the locus coeruleus of rats isolated 30 min after the SC administration of a single dose of (−)-deprenyl. The amount of norepinephrine released from the tissue within 20 min after the administration of different doses of (−)-deprenyl was measured according to Knoll and Miklya (10). Vertical lines show SEM. Paired Student's t test. $*P < .01$.

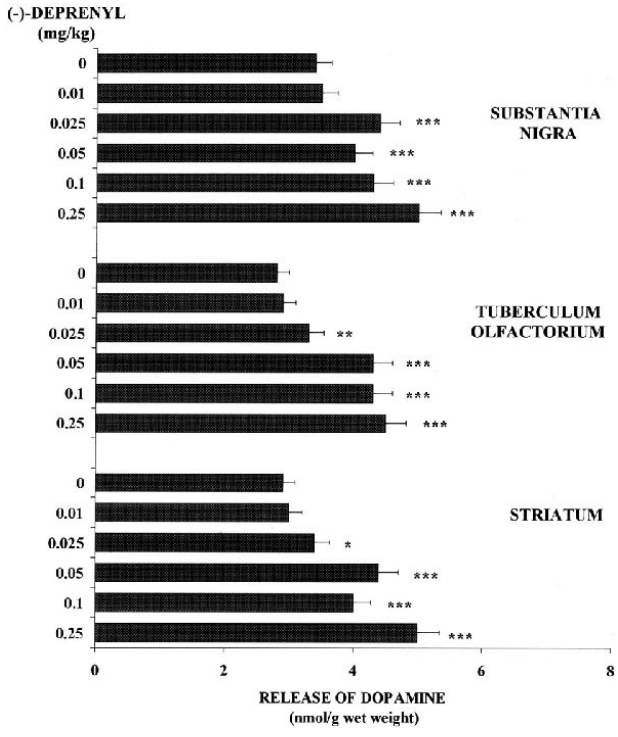

Fig. 4. The significant enhancement of the release of dopamine from the substantia nigra, tuberculum olfactorium, and striatum, respectively, of rats isolated 30 min after the SC administration of a single dose of (−)-deprenyl. The amount of dopamine released from the tissue within 20 min after the administration of different doses of (−)-deprenyl was measured according to Knoll and Miklya (10). Vertical lines show SEM Paired Student's t test. $*P < .05$, $**P < .02$, $***P < .01$.

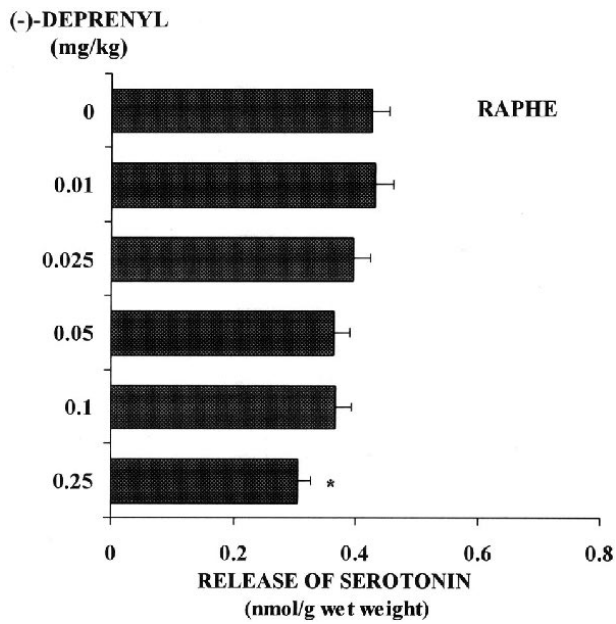

Fig. 5. Lack of the enhancement of the release of serotonin from the raphe of rats isolated 30 min after the SC administration of a single dose of (−)-deprenyl. The amount of serotonin released from the tissue within 20 min after the administration of different doses of (−)-deprenyl was measured according to Knoll and Miklya (10). Vertical lines show SEM. Paired Student's t test was used for statistical analysis. None of the applied doses of (−)-deprenyl enhanced the release of serotonin significantly; the highest dose decreased the release significantly. $*P < .05$.

enhancer substance free of the MAO-B inhibitory property (11). (−)-1-Phenyl-2-propylaminopentane [(−)-PPAP] is our reference substance with this pharma- cological profile.

(−)-BPAP: The Tryptamine-Derived Representative Synthetic Enhancer Substance. The discovery that tryptamine is also an endogenous enhancer substance (2) opened the way for the synthesis of a new family of enhancer compounds unrelated to PEA and the amphetamines, and *R*-(−)-1-(benzofuran-2-yl)-2-propylaminopentane [(−)-BPAP] was selected as the reference compound for further studies (12). (For details of its chemistry see 13 and 14.)

The *in vivo* dose-dependent enhancer effect of (−)-BPAP is illustrated on noradrenergic neurons (Fig. 6), dopaminergic neurons (Fig. 7), and serotonergic neurons (Fig. 8). A comparison of the enhancer effect of (−)-BPAP and (−)-deprenyl shows (i) the substantially higher potency of (−)-BPAP than (−)-deprenyl in enhancing the activity of the catecholaminergic neurons; (ii) the characteristic bell-shaped dose- response curve of the enhancer effect of (−)-BPAP on the noradrenergic neurons (Fig. 7) and serotonergic neurons (Fig. 8); (iii) the highly potent

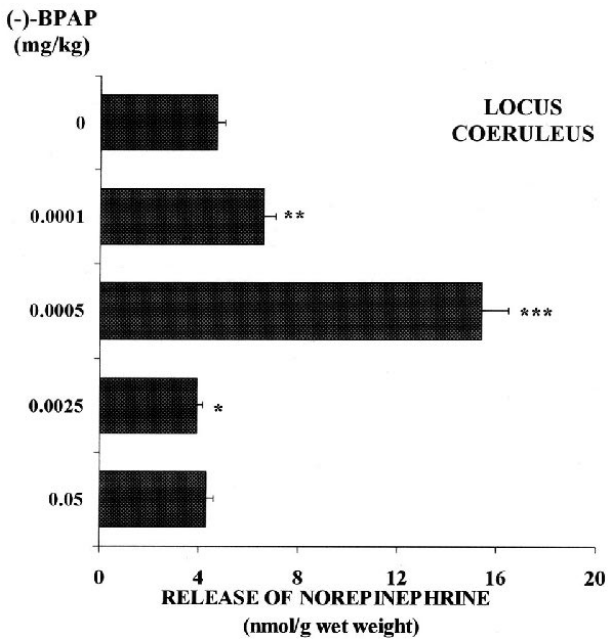

Fig. 6. The significant enhancement of the release of norepinephrine from the locus coeruleus of rats isolated 30 min after the SC administration of a single dose of (−)-BPAP. The amount of norepinephrine released from the tissue within 20 min after the administration of different doses of (−)-BPAP was measured according to Knoll and Miklya (10). Vertical lines show SEM. Paired Student's t test. $*P < .05$, $**P < .01$, $**P < .001$.

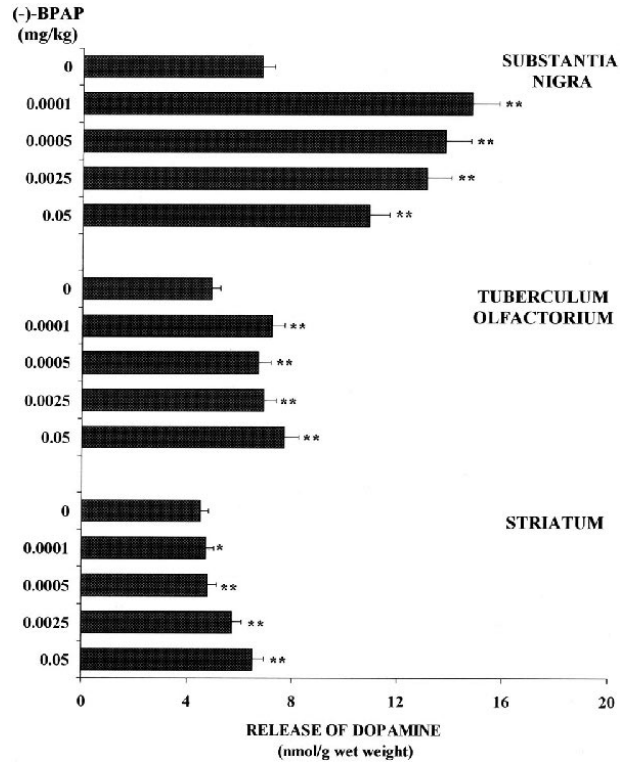

Fig. 7. The significant enhancement of the release of dopamine from the substantia nigra, tuberculum olfactorium, and striatum, respectively, of rats isolated 30 min after the SC administration of a single dose of (−)-BPAP. The amount of dopamine released from the tissue within 20 min after the administration of different doses of (−)-BPAP was measured according to Knoll and Miklya (10). Vertical lines show SEM. Paired Student's t test. $*P < .05$, $**P < .01$.

enhancer effect of (−)-BPAP (Fig. 5) and the lack of this effect of (−)-deprenyl (Fig. 8) on the serotonergic neurons in *in vivo* experiments.

In a recent study the effect of (−)-BPAP was compared to that of the known stimulants of catecholaminergic or serotonergic neurons (desmethylimipramine, fluoxetine, clorgyline, lazabemide, pergolide, bromocriptine) on electrical stimulation induced release of the labeled transmitters from the isolated brain stem of rats following the incorporation of [^{3}H]-norepinephrine, [^{3}H]-dopamine, or [^{3}H]-serotonin by preincubation into the transmitter stores. The study confirmed the selectivity of the enhancer effect of (−)-BPAP (15).

ANALYSIS OF THE NATURE AND PHYSIOLOGICAL SIGNIFICANCE OF THE ENHANCER REGULATION

Innate and Acquired Drives

To analyze the physiological significance of the enhancer regulation in the mammalian brain, we need to sum up the drives that keep the mammalian organism working as a highly sophisticated, goal-oriented entity.

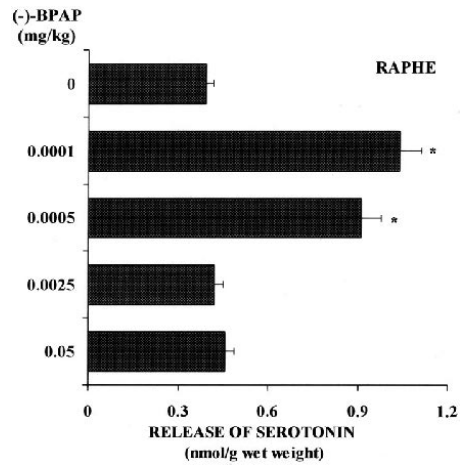

Fig. 8. The significant enhancement of the release of serotonin from the raphe of rats isolated 30 min after the SC administration of a single dose of (−)-BPAP. The amount of serotonin released from the tissue within 20 min after the administration of different doses of (−)-BPAP was measured according to Knoll and Miklya (10). Vertical lines show SEM. Paired Student's t test. $*P < .01$.

Innate Drives for Reaching a Limited Number of Indispensable (Life-Important) Goals. Drives needed for the survival of the individual are (i) the urge to maintain internal stability (homeostasis); (ii) the urge to keep away from or to get rid of anything that is endangering or unpleasent; and (iii) the urge to obtain water and food. Drives needed for the survival of the species are (i) the urge to copulate and (ii) the urge to nurture offspring.

The topic of brain mechanisms in service of the innate drives constitute the main body of the practically immense literature on behavioral physiology and endocrinology. Innate drives are obviously primarily based on the mesencephalic enhancer regulation.

Acquired Drives for Reaching an Unlimited Number of Dispensable Goals. The potentiality to acquire an unsuppressable urge for a goal that is unnecessary for survival of the individual or the species is the most sophisticated function of the telencephalon. Although the development of an acquired drive is always rooted in one way or another on an innate drive, as soon as the acquired drive fully develops, this relation becomes unrecognizable. Humans are the only living beings whose life is predominantly based on acquired drives.

The telencephalon of some docile animal species (monkey, dog, horse, dolphin, rat, etc.) possesses the ability to build acquired drives under proper conditions. This is, however, just an innate potentiality that remains practically unexploited under natural conditions. Humans recognized this potentiality in ancient times, developed proper methods by trial and error that activated the "sleeping" enhancer regulation in the cortical neurons, and domesticated suitable species.

Physiological Analysis of the Nature of the Mesencephalic and Telencephalic Enhancer Regulation

The "Glass-Cylinder–Seeking" Drive in Rats: A Model to Study the Characteristics of an Acquired Drive. Some docile strains of laboratory rats lend themselves particularly well to the analysis of the formation of an acquired drive and for studying the basic role of an innate drive in the acquisition of an urge for an unnatural goal. In the 1950s we developed a method to build a special acquired urge into the brain of rats, the glass-cylinder–seeking drive (16–21; see 1 for review). Based on an unconditioned avoidance reflex (escape from a hot plate) and using the sound of a shrill bell as a conditioned stimulus, rats were trained to search for and jump to the rim of a glass cylinder that also had openings at the top, bottom, and side.

In the training procedure the rat was pushed through the side opening of the glass-cylinder standing on a metal plate heated to 60°C, and the rat escaped from the hot plate by jumping onto the top of the glass-cylinder. The jumping reflex was elicited for a couple of weeks three times daily on 10–50 occasions at 10-s intervals with bell and heat stimulation. After a short training period an inestinguishable conditioned reflex developed and the rat displayed the jumping reflex without heat stimulation 100 times in succession (16–18). This was a transient stage leading to the manifestation of the glass-cylinder–seeking drive (see 1; Chapter 4, for review).

The best-performing rats acquired the glass-cylinder–seeking drive in a stable manner, possessing thereafter this unnatural urge for a lifetime. These rats showed the same high-grade adaptability and readiness in overcoming different obstacles when reaching the goal as the ones influenced by innate drives, such as hunger or sexual desire (19–21).

In the most efficiently trained rats the acquired drive was so powerful that it suppressed innate drives. When a properly trained rat was deprived of food for 48 h and then put in the usual setup that contained the glass cylinder, but food was also available and the shrill bell rang, the rat looked for the glass-cylinder and left the food untouched. We observed the same when a sexually fully active glass-cylinder–seeking male rat could choose between a receptive female and the glass cylinder in the usual setup when the shrill bell rang. The male looked for the glass cylinder and neglected the receptive female.

Urged by the acquired drive, glass-cylinder–seeking rats built with the same extreme rapidity as rats driven by hunger chains of conditioned reflexes consisting hundreds of newly acquired associations. By changing the position of the glass cylinder in the setup, the chain of the conditioned reflexes extinguished as rapidly as in the case of innate drives, and the rat rapidly built a new chain of conditioned reflexes according to the need (20,21). This function elucidates the real physiological role of the extinguishable conditioned reflexes as tools that allow proper accomodation to the rapidly changing outside world. (For reviewing the acquisition and the nature of the glass-cylinder-seeking drive in rats see 1.)

An analysis of this unnatural drive led to the conclusion that during the training procedure proper cortical neurons acquire the ability to get into a special state of activation (the cortical representation of the

drive). This ability of the cortical neurons is an innate, "sleeping" potentiality. Only human intervention activated this regulation that had never functioned in the proper cortical neurons during the lifetime of the rat under natural conditions.

Specific Activation (Active Focus): The Physiological Basis of a Drive. We described earlier the essence of both the innate and acquired drives as a state of specific activation (active focus) in a special population of subcortical and cortical neurons, respectively (see 1, Fig. 11). Now, in the light of the enhancer regulation, we may define the active focus as the endogenous enhancer substance–induced state of dynamically enhanced activity of a special population of mesencephalic and telencephalic neurons. This enhanced state of performance persists until the goal has been reached.

In case of the innate drives the enhancer regulation in the mesencephalon is primarily responsible for the formation of the subcortical active focus and maintains the enhanced orienting-searching reflex activity until the goal is reached. Though lifelong operation the innate drive is repeatedly urging the individual to reach the same goal, with the natural conditions always changing. This leads necessarily to the involvement of cortical neurons in the process (unavoidable conditioning), and there is no innate drive that is not deeply modified by chains of extinguishable conditioned reflexes serving increasingly efficient performance.

In the case of the acquired drives the essence of the complicated behavioral performance is the activation of the enhancer regulation in a special population of cortical neurons, forming a cortical active focus that keeps the organism in action until the goal is reached. But whatever the cortically determined goal is, it cannot be reached without a strong orienting-searching performance resulting from properly enhanced mesencephalic (mainly dopaminergic) activity. Accordingly, an acquired drive brings the mesencephalic system into the same state of enhanced activity as do innate drives.

The catecholaminergic machinery in the mesencephalic system deserves special consideration. Independently from any behavioral performance, the continuous perception of the outside and the inside, the puzzling world of the innate (unconditioned) reflexes, the maintainance of homeostasis, keeps the brain by itself active. Accordingly, the "engine of the brain" is incessantly in motion; catecholamines that influence—activate or inhibit—billions of neurons, are continuously released in the mesencephalon. There are no synaptic contacts between the catecholaminergic neurons and those influenced by the catecholamines in the brain; thus the amount of catecholamines released within a given time interval will determine the extent of the catecholaminergic influence on the whole brain. The enhancer regulation capable of changing dynamically according to the need the amount of free catecholamines in the brain plays a determinant role in survival.

To test the validity of the working hypothesis that in any form of goal-seeking behavior the catecholaminergic and serotonergic neurons work on a higher activity level, we compared the performance of these neurons in the brain of sated and food-deprived rats. We measured in a special open field the orienting-searching reflex activity of rats deprived of food for 48 and 72 h, respectively, and thereafter isolated proper discrete brain areas from the mesencephalon and measured the amount of norepinephrine, dopamine, and serotonin released from the tissue samples into the organ bath. The orienting-searching reflex activity of the rats increased proportionally to the time elapsed from the last feed and the amount of dopamine released from the striatum, substantia nigra, and tuberculum olfactorium, that of norepinephrine released from the locus coeruleus and that of serotonin released from the raphe increased in the hungry rats proportionally to the time of fasting. For example, the amount of dopamine released from the substantia nigra of sated rats (4.62 ± 0.20 nM/g wet weight) increased in rats deprived of food for 48 and 72 h, to 5.95 ± 0.37 ($P < .05$) and 10.67 ± 0.44 ($P < .01$), respectively (22).

Pharmacological Analysis of the Enhancer Regulation Using (−)-BPAP as a Specific Experimental Tool

Detection of Two Forms of the Enhancer Regulation in the Mesencephalic Neurons. (−)-BPAP is at present the most selective and potent experimental tool to get information about the enhancer regulation in the mesencephalon. The enhancer effect can be detected after the SC administration of low amounts of (−)-BPAP (see 12, Table 2), as well as after the addition of the substance into the organ bath of freshly isolated discrete mesencephalic brain areas (see 12, Table 3). Enhancer substances stimulate the enhancer-sensitive neurons in the mesencephalon in a peculiar manner. For example, Fig. 9 shows the bi-modal concentration/effect curve characteristic to the enhancer effect of (−)-BPAP added to the isolated locus coeruleus of rats. We find two bell-shaped concentration/effect

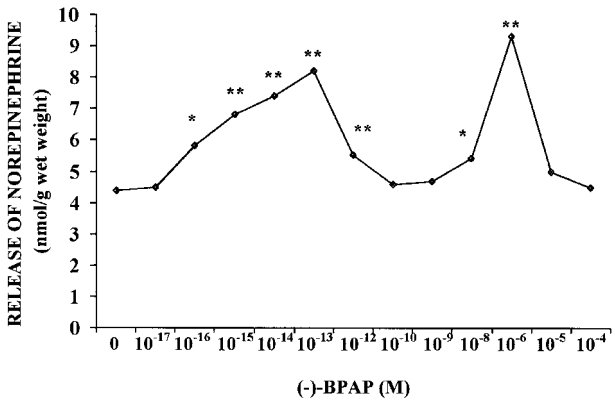

Fig. 9. The bi-modal bell-shaped concentration/effect curve characteristic to the enhancer effect of (−)-BPAP on the isolated locus coeruleus of rats. (−)-BPAP was given to the organ bath of the quickly removed locus coeruleus. Eight rats were used for the analysis of each concentration. The amount of norepinephrine released within 20 min from the tissue in the presence of different concentrations of (−)-BPAP was measured according to Knoll and Miklya (10). Paired Student's t test. $*P < .01$, $**P < .001$.

curves. One in the low nanomolar range, with a peak effect at 10^{-14} M concentration, clearly demonstrates the existence of a highly sophisticated, specific form of enhancer regulation in noradrenergic neurons. The second bell-shaped concentration/effect curve at higher micromolar range, with a peak effect at 10^{-6} M concentration, shows the operation of a hundred million times less-sensitive, nonspecific form of the enhancer regulation in these neurons (see 23 for details).

We experienced, in a number of studies on rats (16–21,24,25), the validity of the common knowledge that there is great individual variation in sexual activity and learning performance in any random population of mammals of the same strain. As will be discussed later in more detail, the discovery of the bell-shaped concentration/effect curve of the enhancer substance in the low nanomolar concentration range offers now, for the first time, a reasonable explanation for this phenomenon.

Detection of the Two Forms of the Enhancer Regulation on Isolated Brain Cells in Culture. (−)-BPAP proved to be a proper experimental tool for detecting the presence and analyzing the nature of the enhancer regulation on isolated brain cells.

Considering the role of the mesencephalic neurons in goal-seeking behavior and collating this experience with the finding that the performance of the catecholaminergic and serotonergic neurons were significantly enhanced in rats *in vivo* with 0.0001 mg/kg (−)-BPAP (see 12, Table 2), and *in vitro* at 10^{-14} M concentration (see 12, Table 3), it was reasonable to assume that this highly sophisticated form of enhancer regulation is the physiological mechanism in the mesencephalon responsible for a drive. We may also assume that the enhancement of nerve cell performance elicited by (−)-BPAP in the high micromolecular concentration range is from a physiological point of view a nonspecific effect, obviously unrelated to behavioral performances.

This view was substantiated by studies with (−)-BPAP on isolated single brain cells in culture: (i) two studies on glia cells (26,27), (ii) one study on mesencephalic neurons (12) and (iii) two studies on telencephalic neurons (28 and see Fig. 10 and 11 in this study).

Study on Cultured Glia Cells. Neuroglia play an important physiological role in the brain and modulates the function of neurons in a complex manner; it does not participate, however, in the realization of goal-seeking behavior. Thus it was of crucial importance to test the effect of (−)-BPAP on the performance of glial cells. Two studies were performed with (−)-BPAP on cultured mouse astrocytes (26,27).

As a quantitatively measurable specific function of glial cells, the rate of synthesis of three neurotrophic factors (nerve growth factor [NGF], brain-derived neurotrophic factor [BDNF], and glial cell line–derived neurotrophic factor [GDNF]) was measured. In the Ohta et al. (26) study, the enhancer effect of (−)-BPAP was measured in the high macromolecular concentration range only. The authors found the amounts of NGF, BDNF, and GDNF secreted from astrocytes into the culture medium increased by up to 120, 2, and 7 times, respectively, higher than those of the control by treatment with 0.35 mM (−)-BPAP for 24 h. The (−)-BPAP induced increased production of NGF and GDNF was inhibited by concomitant administration of actinomycin D, given for transcription blockade. (−)-BPAP treatment increased the mRNA expression of NGF, BDNF, and GDNF. The results of this study proved that the nonspecific form of the enhancer regulation operates also in glial cells.

In the second study the effect of (−)-BPAP was tested in a range of 10^{-15} to 5×10^{-4} M concentration. This study corroborated the finding of the first one. The synthesis of NGF was significantly enhanced in the high micromolar concentration range with a peak effect at 10^{-4} M concentration, whereas 5×10^{-4} M was ineffective. (−)-BPAP acted similarly on the synthesis of BDNF (with a peak effect of 10^{-4} M concentration) and on the synthesis of GDNF (with a peak effect of 10^{-4} M concentration) (27). But the crucially important step forward was the proof that, as expected,

(−)-BPAP was ineffective in the low nanomolar concentration range. Thus the specific form of the enhancer regulation was not detectable in glial cells.

This finding substantially supports the view that the specific form of the enhancer regulation stimulated by (−)-BPAP in the low nanomolar concentration range is the behaviorally important form, whereas the enhancer effect of (−)-BPAP in the micromolar concentration range is nonspecific, insignificant from a behavioral aspect. Nevertheless, the significant enhancement of the synthesis of neurotrophic factors by (−)-BPAP is a remarkable pharmacological effect. An analysis of its potential therapeutic value might be a reasonable subject for clinical research in the future.

Study on Cultured Mesencephalic Neurons. The first analysis of the enhancer regulation on cultured neurons using racemic BPAP as a specific experimental tool was performed on rat hippocampal cells (12).

To elicit cell death the cultured rat hippocampal neurons were treated with β-amyloid$_{25–35}$. BPAP exerted its enhancer effect in the characteristic bi-polar manner, with bell-shaped concentration/effect curves. The peak effect was reached at 10^{-14} M concentration in the low nanomolar concentration range, and at 10^{-8} M concentration in the higher micromolar concentration range (see 12, Fig. 5). Because of the neurotoxic effect of β-amyloid$_{25–35}$, no more than 20% of the cells, obviously the high-performing cells, survived this attack. BPAP enhanced significantly the performance of the neurons, and in the presence of the optimum concentration (10^{-14} M) about 70% of the cells survived. (−)-BPAP enhanced exactly in the same bi-polar manner and in the same concentration range the activity of the catecholaminergic and serotonergic neurons in experiments performed on isolated discrete mesencephalic regions (see 12, Table 3).

The studies with (−)-BPAP performed on noradrenergic, dopaminergic, serotonergic, and hippocampal neurons proved unequivocally the operation of a highly sophisticated form of enhancer regulation in the mesencephalic neurons. This is in excellent agreement with the determinative physiological role of midbrain neurons in goal-seeking behavior.

Study on Cultured Telencephalic Neurons. The first study of the enhancer effect on cultured telencephalic neurons was performed with (−)-BPAP on a primary culture of rat cerebral cortex. In this experiment the rapid cell death of the cortical neurons was measured in serum-free culture. It was shown that in a low-cell-density culture cortical neurons rapidly die under serum-free condition in an inverse density-dependent manner. (−)-BPAP, as first shown by Hamabe et al. (see 28, Fig. 2), significantly protected the cortical neurons against serum-free condition–induced cell death in the high micromolecular concentration range. The protective effect of (−)-BPAP, with a peak effect at 10^{-6} M concentration, is shown in Fig. 10A. However, in striking contrast to the finding on cultured rat hippocampal neurons (see 12, Fig 5), (−)-BPAP did not exert in the nanomolar concentration range an enhancer effect on the cultured cortical neurons. This is shown in Fig. 10B.

The striking difference between the cultured rat mesencephalic and telencephalic neurons in their

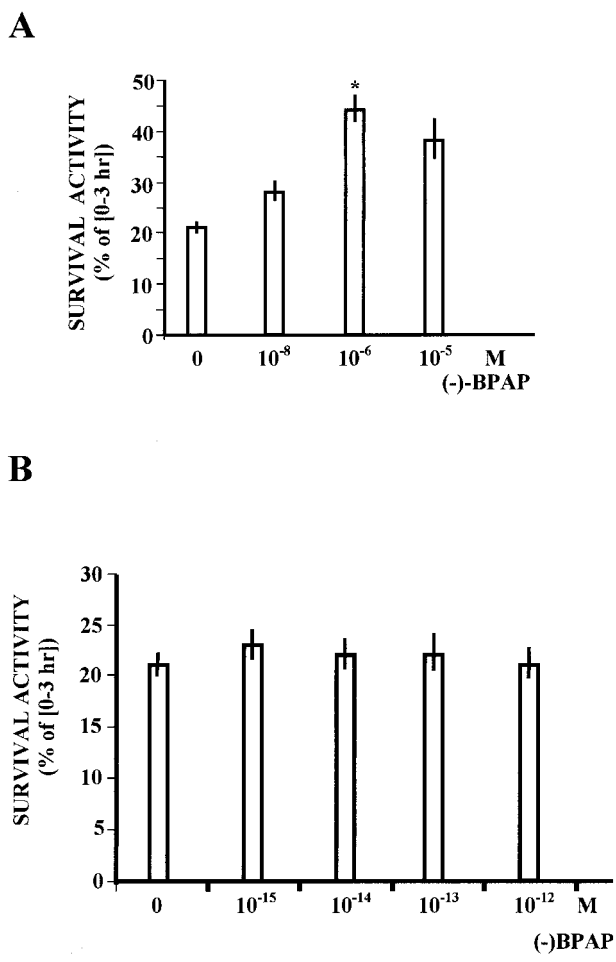

Fig. 10. A, Protective effect of (−)-BPAP in the high micromolar concentration range, with a peak effect at 10^{-6} M concentration, against serum-free condition–induced cell death in low-cell-density culture of the cerebral cortex from E17 rats. **B,** Lack of a protective effect of (−)-BPAP under the same conditions in the low nanomolar concentration range. Experiments were carried out in triplicate. Data are the mean ± SEM from six independent experiments. The data were analyzed using Student's t test after multiple comparisons of ANOVA. $*P < .05$ compared with results in vehicle treated culture. See 28 for methodology.

sensitivity toward (−)-BPAP seems to be a telltale sign of the basically different physiological function of the cortical and subcortical neurons. Collating our results with (−)-BPAP on cultured neurons of rats and our experiments with the development of the glass-cylinder–seeking drive (16–21), it seems reasonable to explain the phenomena described above, as follows.

The mesencephalic neurons, responsible for the innate drives, possess an ever-active sophisticated enhancer regulation. The enhancer receptors are supplied with endogenous ligand(s). In contrast, the cortical neurons, responsible for the acquired drives, are born with a specific enhancer receptor, but the enhancer regulation, because of the absence of the specific ligand to this receptor, is sleeping. In response to proper training the cortical neurons acquire the ability to transform themselves, when needed, into the state of enhanced activity. The course of acquisition of the glass-cylinder–seeking drive and the lifelong operation of this urge thereafter, speaks clearly in favor of the neuron's inborn ability to create its own specific ligand in response to proper long-term stimulation (proper training) and to the ability of the properly trained neuron to produce this ligand according to the need. This is the basis of the acquired drive. To draw a parallel, the mesencephalic neuron is a slow-combustion stove, the cortical neuron of a docile species capable of acquiring unnatural drives is a stove ready for lighting. It just requires kindling. Proper training ignites the stove and transforms it to a slow-combustion one.

To test this difference between the mesencephalic and telencephalic neurons of rats *in vivo,* we performed a properly designed study in the shuttle box. As shown earlier, very low doses of (–)-BPAP antagonized tetrabenazine-induced inhibition of learning of the rat in the shuttle box (12). As tetrabenazine depletes the catecholamine stores in the brain, the antagonistic effect of very low doses of (−)-BPAP was clear proof for the *in vivo* operation of the specific form of the enhancer regulation in the catecholaminergic neurons.

Because the acquisition of a conditioned reflex is a cortical function, we investigated the effect of (−)-BPAP on this function. In the shuttle box the acquisition of a two-way conditioned avoidance reflex (CAR) was analyzed for 5 consecutive days. The rat was put in a box separated inside by a barrier with a small gate in the middle, and the animal was trained to cross the barrier under the influence of a conditioned stimulus (CS, light flash). If it failed to respond within 5 s, it was punished with the unconditioned stimulus (US), a footshock (1 mA). If the rat failed to respond within 5 s to the US, it was noted as escape failure (EF). One trial consisted of a 15-s intertrial interval (IR), followed by a 15-s CS. The last 5 s of CS overlapped the 5-s US. At each learning session, the number of CARs, EFs, and IRs were automatically counted and evaluated by multiway ANOVA.

To test a compound's ability to enhance the acquisition of CARs in the shuttle box, we need to select proper training conditions. In the case in which the rat was trained with 100 trials per day, the acquisition of CARs reached an 80% level and the EFs approached or reached the zero level. To demonstrate the highly significant enhancer effect of (−)-BPAP on the catecholaminergic neurons *in vivo,* we trained the rat with 100 trials per day, blocked the acquisition of CARs by pretreating the rats with tetrabenazine, and restored learning ability with the simultaneous administration of (−)-BPAP. Table I shows that (−)-BPAP antagonized the effect of tetrabenazine in the rats.

To detect the enhancer effect of (−)-BPAP on learning, we trained the rats with 20 trials per day. Whereas the percentage of CARs in rats trained with 100 trials per day was 77.13 ± 8.47 on the 5th day of the training, it was only 8.50 ± 2.47 in rats trained with 20 trials per day. Table II shows the effect of eight doses of (−)-BPAP, ranging from 0.000001 to 10 mg/kg on the learning ability of rats in the shuttle box. None of the doses exerted a significant effect on learning, clearly proving that (−)-BPAP had no enhancer effect on the cortical neurons *in vivo*.

The second study of the enhancer effect on cultured telencephalic neurons was performed on cortical cells from 8-day-old chicken embrios (Lohman brown hybrid). Up to the present this was the only study on nonmammalian brain cells. (−)-BPAP detected the operation of both the specific and nonspecific form of the enhancer regulation in the cortical neurons of this avian species. The performance of the cortical neurons was enhanced in the low nanomolar concentration range of (−)-BPAP, with a peak effect at 10^{-14} M concentration (Fig. 11). As shown above, (−)-BPAP enhanced also the performance of rat mesencephalic neurons with exactly the same peak concentration.

Consideration about the Nature and Physiological Significance of the Telencephalic Enhancer Regulation

The remarkable difference in the sensitivity for (−)-BPAP between the isolated cortical cells of the rat and the chicken deserves serious consideration.

Table I. Because of Its Enhancer Effect on Catecholaminergic Neurons (−)-BPAP Antagonized Tetrabenazine-Induced Learning Deficit in Rats Trained in the Shuttle Box

Series no.	Compound (mg/kg)	Tetrabenazine (mg/kg)	Percentage of CARs	Percentage of EFs	Number of IRs
1	Saline (−)-BPAP	—	77.13 ± 8.47	6.00 ± 5.72	34.25 ± 11.21
2	—	1	5.00 ± 3.30	61.50 ± 13.80	5.83 ± 2.18
3	0.05	1	46.88 ± 14.15*	17.88 ± 9.30***	9.25 ± 2.81
4	0.10	1	46.38 ± 8.75***	7.38 ± 4.34****	6.75 ± 1.03
5	0.25	1	59.00 ± 12.62***	5.25 ± 2.13****	16.75 ± 5.74
6	0.50	1	70.38 ± 10.73****	1.38 ± 1.02****	8.50 ± 2.83
7	1.00	1	87.75 ± 1.95****	0.13 ± 0.13****	27.38 ± 4.49**
8	2.50	1	79.75 ± 7.03****	1.38 ± 1.12****	24.50 ± 9.19*
9	5.00	1	92.00 ± 2.47****	0.00****	57.88 ± 19.37*
10	10.00	1	92.00 ± 2.46****	0.00****	68.33 ± 26.46*

Note: Tetrabenazine or the combination of tetrabenazine + (−)-BPAP were administered SC 60 min before daily measurement.
CAR = conditioned avoidance response, EF = escape failure, IR = intersignal reaction. Rats (in each group 4 males and 4 females) were trained at 100 trials daily for 5 days in the shuttle box.
The performance on the fifth day of training is shown in the table.
Significant to tetrabenazine (ANOVA): $*P < .05$, $**P < .02$, $***P < .01$, $****P < .001$.

Though the experimental tools used for eliciting cell death were different in the two studies, β-amyloid$_{25–35}$ was used in the chicken experiment (Fig. 11) and serum-free condition in the rat study (Fig. 10), it seems unreasonable to make this difference culpable for the unexpected behavior of the cortical cells. It seems much more reasonable that we hit upon the basic difference in the function of the cortical neurons that made the chicken a markedly dull species in the learning tests and the rat clever in experimental studies, an exclusively important role in the development of behavioral sciences.

Table II. Because of Its Ineffectiveness on Cortical Neurons (−)-BPAP Did Not Enhance the Learning Performance of Rats Trained in the Shuttle Box

Series no.	(−)-BPAP mg/kg	Percentage of CARs	Percentage of EFs	Number of IRs
1	Saline	8.50 ± 2.47	0.75 ± 0.62	1.88 ± 1.01
2	0.000001	6.13 ± 1.99	1.25 ± 0.65	4.00 ± 2.65
3	0.00001	4.38 ± 2.08	3.25 ± 1.56	3.63 ± 1.46
4	0.00005	5.88 ± 2.44	2.38 ± 1.96	2.50 ± 1.02
5	0.0001	12.75 ± 2.18	0.63 ± 0.63	1.25 ± 1.68
6	0.0005	9.63 ± 2.07	0.63 ± 0.42	6.50 ± 3.08
7	0.025	8.50 ± 2.48	2.25 ± 1.16	2.88 ± 1.39
8	0.05	8.63 ± 2.13	0.00	4.38 ± 2.34
9	0.1	6.75 ± 2.96	2.13 ± 2.13	2.13 ± 0.61
10	1.0	8.50 ± 2.63	0.00	4.25 ± 1.82
11	10.0	0.63 ± 0.42	1.13 ± 0.74	2.88 ± 1.26

Note: (−)-BPAP was administered SC 60 min before daily measurement.
CAR = conditioned avoidance response, EF = escape failure, IR = intersignal reaction. Rats (in each group 4 males and 4 females) were trained at 20 trials daily for 5 days in the shuttle box.
The performance on the fifth day of training is shown in the table.
Significancy to saline was calculated according to ANOVA, in all cases $P > .05$.

The previously discussed ability of the rat to acquire the glass-cylinder–seeking drive is an excellent example to show that the cortical neurons in the rat possess the ability to properly change their functional state in response to training in a manner that is not common in the animal kingdom. The mouse, a rodent closely related to the rat, and a much more docile species than the chicken, was found to be unable to build the glass-cylinder–seeking drive (see 1 for review). It was shown by Berta Knoll (29) that the mouse was even unable to acquire the inextinguishable form of the conditioned avoidance reflex, the functional stage preceding the acquisition of the glass-cylinder–seeking drive.

Brains of members of the same strain are undeniably equal in value, because the device is the same. This is also true for the species capable to acquire new drives. However, because of the extreme differences in life conditions that primarily determine the realm of the acquired drives, and because of the extreme individual variation in learning performances, it is unpredictable which minuscule part of the practically immense inborn potentialities will *de facto* be utilized. Because of the practically even natural living conditions, there are, in contrast to humans, very small

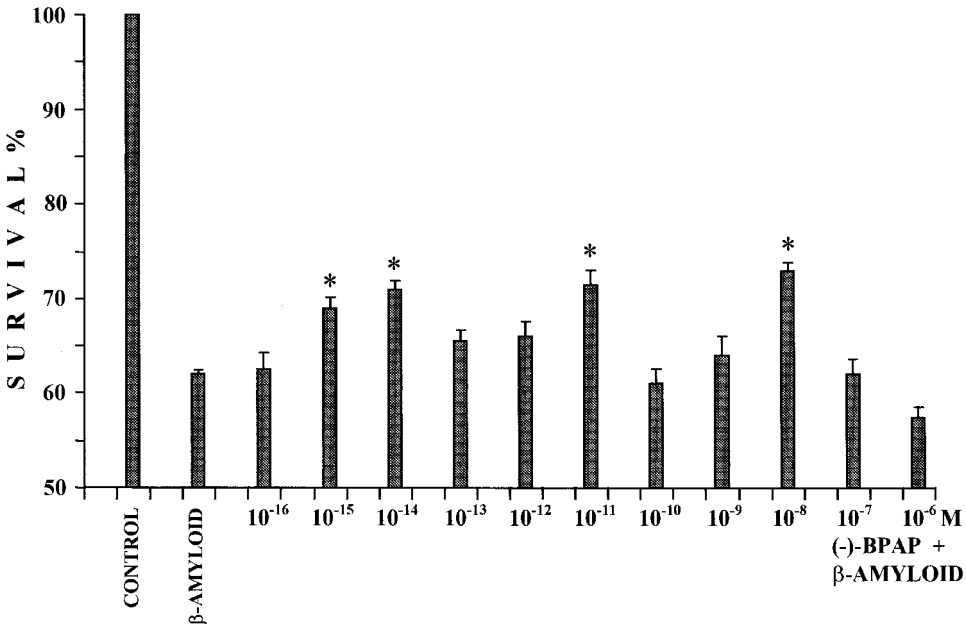

Fig. 11. The protective effect of (−)-BPAP against β-amyloid$_{25–35}$–induced cell-death on isolated cortical neurons from 8-day-old chicken embryos (Lohman brown hybrid) duration of one single experiment: 10 days. (−)-BPAP has been added to the culture at the first day *in vitro.* Lesioning with β-amyloid$_{25–35}$ preaggregated for at least 72 h. Concentration and stock solution 1 mM, lesioning with 10 μl of the stock solution. Columns in the figure given in percent of the unlesioned control (100%), represent the mean viability ± SEM, from two independent experiment performed at 2 days with two 96-well plates and six to eight identical wells/concentration and substance. Statistical analysis: two-tailed Student's t test for two means. $*P < .05$.

differences in the life of the individuals of the same species in the animal kingdom.

An individual strives necessarily to build those forms of acquired drives that demand the shortest training time with the lowest investment of energy. It is the plastic description of this phenomenon that individuals select their activities according to their talent.

We realized in our longitudinal studies on rats analyzing, on the one hand, the functioning of the (mesencephalic) hunger and sexual drives, and on the other hand, the (telencephalic) glass-cylinder–seeking drive, that in response to proper training the cortical neuron gets through four stages in succession, until the achievable highest functional level, the manifestation of the specific form of enhancer regulation, will be reached. We may classify cortical neurons according to the highest functional level they have ever reached during the lifetime of the individual in four groups, as follows.

Group 1: Cortical Neurons That Were Never Properly Trained. These neurons, if they were used at all, just reacted accidentally to their innately specific stimulus, but were never properly trained to reach even the functional state needed for the acquisition of an extinguishable conditioned reflex. Because the mammalian brain is supplied with an extremely high number of cortical neurons, only a small part of them can be properly trained during the short lifetime of the organism. The overwhelming majority of the available population remains obviously unutilized.

Group 2: Cortical Neurons That Were Trained Until an Extinguishable Conditioned Reflex Developed. The essence of training is the stimulation of these cortical neurons with their specific stimulus simultaneously with the precipitation of an unconditioned reflex. This functional state was for sure the most thoroughly studied variation in the history of brain research. In our experiments the physiological significance of this functional state was illustrated in the quick adaptation of the glass-cylinder–seeking rats that built and dropped, according to the need, long chains of rapidly extinguishable conditioned reflexes (tool reflexes) enabling them to easily reach the goal despite of substantial changes in the environment (see 1 for details). Pavlov himself, and, in an exaggerated manner, his followers, tried to force the doctrine that the totality of the higher nervous activity can be explained by the aid of this mechanism.

Group 3: Cortical Neurons That Were Trained until an Inextinguishable Conditioned Reflex Developed. This was found to be a stable intermediate stage in the course of the training procedure aiming to develop an acquired drive. It was shown by Kelemen et al. (30) that this stage can sharply be differentiated by EEG from an extinguishable conditioned reflex.

Group 4: Cortical Neurons That Were Trained until They Manifested Their Specific Enhancer Regulation and as a Consequence of It a New Drive Was Acquired. The essence of training is the development of a fully active enhancer regulation in a proper population of cortical neurons (in the cortical representation of the drive).

The learning-induced sequence of events in trained cortical neurons make it clear that for a docile mammal, ready to acquire unnatural drives, life means the continuous modification of behavior through practice, training, or experience. This modification is based on the transition of cortical neurons from the naive state into a functionally more sophisticated state. A human cortex is, at birth, comparable with a book consisting of about hundreds of billions of empty pages. This is an immense quantity, and life is obviously to short to scribble over this book. Every mammalian organism is determined in any moment by the number of neurons that changed their functional state until this date, and in case of humans the self is determined primarily by the number of neurons that reached the highest functional level of activity and belong already into Group 4.

Domestication of animals proves that humans realized in ancient times the ability of some animal species to acquire drives for unnatural goals, and made a good use of it. There is no reason to deny that the same telencephalic enhancer regulation is responsible for any kind of acquired drives, and there is no difference in this respect between the rat's glass-cylinder–seeking drive or the most sophisticated form of the human acquired drives, the unique interpersonal communication (talking, writing, reading). There can be no doubt, however, that human's performance is qualitatively different from that of docile animals. This is a typical example of the transition of quantity into quality. There is obviously an enormous quantitative difference between the most docile animals and humans in the ability of their cortical neurons to activate the sleeping enhancer regulation. Only the human telencephalon is capable of making this alteration with ease and high speed. Compared to humans, the ability to acquire a new drive is a rudimentary function in animals.

In our studies aiming to build the glass-cylinder–seeking drive into the brain of rats, we trained hundreds of animals and followed their performance during their postdevelopmental life (16–21). In one series of experiments performed on a random group of 100 2-month-old rats (50 males, 50 females) we developed within a 3-week training period in each animal the inextinguishable conditioned jumping reflex. But out of the 100 rats, only 20% of the population (11 females, 9 males) showed clear-cut signs of a tendency to acquire the glass-cylinder–seeking drive and two of them (1 male and 1 female) finally possessed this drive in a lifelong operating manner. If we compare this performance to the almost unlimited ability of humans to acquire new drives, the qualitative difference in performance is understandable without any compelling need to deny that the mechanism of the telencephalic specific enhancer regulation is essentially the same in the two species. We have just a new example of the general rule in nature that an immense variety of colorful phenomena, in this case the fantastic variation in the outward form of behavioral performances, rests on the operation of a common simple mechanism. Gravitation keeps the whole universe going.

Although any form of an acquired drive is rooted on one of the innate drives, as soon as the new drive develops and operates in an inextinguishable manner, the roots are unrecognizable. Watching, for example, a glass-cylinder–seeking rat in operation, one cannot recognize that this acquired drive is rooted on a simple unconditioned avoidance reflex, the escape from a hot plate.

It seems reasonable to assume that from functional point of view the appearance of species with the ability to acquire drives for unnatural goals was the last crucially important leap in the development of brain organization. In the animal kingdom the development reached its functionally most sophisticated level in the group of anthropoid apes. The mechanism, however, arrived to its perfection in *Homo sapiens,* culminating in speech, the classic, human-specific form of an immense set of acquired drives.

The learning of each word is an inextinguishable conditioned reflex, each sentence a chain of them. These chains are easily and with extreme rapidity changed according to need and serve as tools to reach an immense number of goals. Speech, accomplished with all other forms of interpersonal contacts based on language, the most-sophisticated form of goal-oriented behavior, produced the highest level of human achievement, arts and science and allowed preservation, with higher or lower efficiency, the achievements of

ancestors and created human society, in which each generation stands on the shoulder of the past generations, considering history and envisaging the future.

The Relationship between Enhancer Regulation and the Substantial Individual Variation in Behavioral Performances

We now have a reasonable explanation for the probably most striking feature in behavioral studies with docile animals: the marked individual variation in performance. The development of (−)-BPAP and the experience that the highly sophisticated form of its enhancer effect is expressed by a peculiar bell-shaped dose/response curve, as shown in Fig. 9, offers a self-evident explanation of the extreme individual variation in learning performance, which might reside in the unique dose-dependency of the enhancer effect.

An analysis of the example shown in Fig. 9 supports this assumption. The most effective dose of (−)-BPAP, 0.0005 mg/kg, increased the release of norepinephrine from 4.7 ± 0.10 nM/g (control) to 15.4 ± 0.55 nM/g ($P < .001$), but a 100-times higher dose of (−)-BPAP (0.05 mg/kg) did not change it (4.3 ± 0.25 nM/g) (23). Thus an *optimum* concentration of the enhancer is needed for the *optimum* output of the neuron.

The optimum concentration is the core of the problem. To illustrate it, we quote two examples from our earlier studies, one related to an innate drive and the other to an acquired drive:

In a study we selected sexually high- and low-performing male rats from a population of 1600 rats of the same strain (25). We found 99 high-performing (HP) rats that produced ejaculation in each of the four consecutive weekly mating tests used for selection, and 94 low-performing (LP) rats, unable to produce a single intromission in the four mating tests. We can say that out of the 1600 rats the 99 HP rats produced the enhancer substance inciting the sexual drive at the peak of the bell-shaped concentration/effect curve, whereas the 94 LP rats produced it at an inactive part of the curve. The production of the overwhelming majority of the population (1407 rats) falls between the two extremes.

In a second example, despite the same training procedure, only 2 rats out of 100 acquired a lifelong operating glass-cylinder–seeking drive. Obviously, only these 2 glass-cylinder–seeking rats were lucky enough to mobilize the endogenous enhancer substance always in the optimum concentration.

One brain may work at optimum conditions regarding Performance I, the other one regarding Performance II, etc., *ad infinitum;* thus, talents are different. The life story of a human individual is the history of the acquired drives and their use. It is clear that everyone tends to acquire the best-fitting drives. The common-sense statement that it is easy to teach somebody who has the faculty for doing the work is a plastic description of the mechanism that in any form of goal-seeking behavior success is primarily related to the optimum amount of the endogenous enhancer substance mobilized by the proper cortical cells when needed. In humans, serious psychic problems may be rooted in the discrepancy between the desire to select activities that come naturally to one's brain and the incorrigible conditions that hinder their realization. Accordingly, optimally performing humans are satisfied, well-balanced and happy, frustrated ones search for "ersatz": smoking, drinking, drugs, gambling, overeating, pursuing sexual pleasures, etc., pseudoactivities that substitute for the failing ones.

The Age-Related Decline of the Mesencephalic Enhancer Regulation and the Antiaging Potential of Synthetic Enhancer Substances

Enhancer regulation in the rat brain starts working on a significantly higher activity level at the end of the 3rd week of age, that is, the discontinuation of breast-feeding, the crucially important first step to live separately from the mother (10).

Weaning is obviously the onset of the developmental (uphill) phase of the individual life of the mammalian organism (2,3). The period, characterized by a higher basic activity, lasts until the rat develops full-scale sexual maturity. One of the telltale signs that makes the operation of the mesencephalic enhancer mechanism evident is the enhanced basic activity of the catecholaminergic and serotonergic systems, as measured by the significantly enhanced release of catecholamines and serotonin from discrete brain regions isolated from the brain of rats after weaning. As sexual maturity was reached, this change disappeared and the basic activity of the catecholaminergic and serotoninergic systems returned to the preweaning level (31).

Sexual hormones seem to be responsible for the transition from the developmental, uphill phase of life into the postdevelopmental, downhill period, characterized by the slow age-related decay of brain performance terminated by natural death (see 3, Fig. 6). Weighty arguments speak in favor of the assumption that the slow, continuous age-related decline of the enhancer regulation in the mesencephalic neurons plays a key role in the irresistible decay of behavioral performances with the passing of time.

According to our present knowledge the nigrostriatal dopaminergic neurons, which maintain the enhanced orienting-searching reflex activity indispensable for successful goal-seeking behavior, are the most rapidly aging units in the human brain. Over age 45 the dopamine content of the human caudate nucleus decreases steeply, at a rate of 13% per decade. If dopamine sinks below 30% of the normal level, symptoms of Parkinson's disease appear. About 0.1% of the population over 40 years of age develops Parkinson's disease, and prevalence increases sharply with age. Parkinson's disease is an especially convincing example of an age-related neurological disease because of the extraordinarily fast deterioration of an enhancer-sensitive group of midbrain neurons.

Although the decay of the enhancer regulation starts with the full-scale development of sexual hormonal regulation (31), this does not mean that the sexually mature individual is immediately converted to a significantly lower performer in its fight for existence. Experience (conditioning) ensures a rapid and successful goal-directed performance without the need of high-level specific activation of enhancer-sensitive midbrain neurons. This is nature's most ingenious trick to enhance even in the downhill period the chances for survival. The experienced organism works in an economic manner and reaches its goals with much lower energy investment than the unexperienced one. Nevertheless, an irresistible, progressive age-related decay of the enhancer regulation will gradually weaken the ability to acquire new information, and, as a consequence, the life-important adaptability to a new situation will necessarily be on a progressive decline. Thus, even the most experienced aged organism becomes with the passing of time increasingly vulnerable in its struggle for life.

All in all, there can be little doubt that in the downhill period of life there is an irresistible, physiological decrease in the quality of life resulting from the continuous decline of the mesencephalic enhancer regulation. In the light of the peculiar age-related changes, the concept, first proposed in 1982 (32), to slow brain aging by the lifelong prophylactic medication with a small dose of a safe, specific potent synthetic enhancer substance, starting at the transition from the uphill to the downhill period of life, seems reasonable.

This concept was substantially supported by the longevity study performed with (−)-deprenyl between 1984 and 1988, showing that this drug prolongs life (24). Thereafter a growing number of experimental and clinical studies showed that (−)-deprenyl acts as a unique antiaging drug in both animals and humans. Prophylactic (−)-deprenyl medication slows the physiological age-related decay of the catecholaminergic neurons in the mesencephalon, thereby slowing the decay of behavioral performances with the passing of time and prolongs life (see 3 and 9 for review).

Considering the role of the catecholaminergic brain engine in the activation of the telencephalon, we can say that an animal born with a better engine will be the better-performing, longer-living individual. Indeed, we found that lower-performing rats died significantly earlier than their higher-performing peers (24). We analyzed, therefore, in a more concrete manner the relationship between performance and longevity in the rat (25).

From a large random population of young male rats (n = 1600) we selected the sexually inactive animals (low-performing [LP]; n = 94) and sexually most active rats (high-performing [HP]; n = 99) and treated them with saline and (−)-deprenyl, respectively, until they died. HP rats, selected as the most active copulators, performed significantly better on a learning test and lived significantly longer than their LP peers. For example, saline-treated LP rats lived 134.58 ± 2.29 weeks, whereas their HP peers lived 151.24 ± 1.36 weeks ($P < .001$).

On the other hand, both LP and HP rats treated with (−)-deprenyl performed significantly better in sexual and learning tests and lived longer than the saline-treated rats. For example, the lifetime of (−)-deprenyl–treated LP rats (152.54 ± 1.36 weeks) was significantly ($P < .001$) longer than the lifetime of their saline-treated peers (134.58 ± 2.29 weeks), and HP rats treated with (−)-deprenyl lived 185.30 ± 1.96 weeks, significantly ($P < .001$) longer than their saline-treated peers (151.24 ± 1.36).

HP rats perform in behavioral tests significantly better and live longer than LP rats; thus we may assume that a more efficient enhancer regulation operates in HP rats than in their LP peers. The results of a specially designed study substantially supported this view (33).

Studying the learning ability of rats in the shuttle box, we met with remarkable strain and breed differences in performance. Two breeds of rats, Charles River Wistar [Crl (Wi) Br.] and HSD Wistar [Wistar per LATI (Budapest) Br.], with remarkable difference in learning performance were selected. The rats were trained in the shuttle box with 100 trials per day, and the number of conditioned avoidance responses (CARs), the escape failures to the unconditioned stimulus (EFs), and the intersignal reactions (IRs) were counted and evaluated by multiway ANOVA.

Rats of the Crl (Wi) breed proved to be the LP animals and rats of the Wistar per LATI (Budapest) breed the HP ones. The HP rats produced higher number of CARs ($P < .001$), lower number of EFs ($P < .05$), and higher number of IRs ($P < .01$) than the LP rats. Significantly higher amounts of norepinephrine from the locus coeruleus and serotonin from the raphe were released in the HP than in the LP rats ($P < .01$). There was no difference between HP and LP rats in the amount of dopamine released from the striatum, the substantia nigra, and the tuberculum olfactorium. Remarkably, 1 mg/kg (−)-PPAP, a (−)-deprenyl–derived enhancer substance devoid of the MAO-B inhibitory potency of its parent compound, fully antagonized tetrabenazine-induced learning depression in HP rats and was ineffective in LP rats.

The data proved that in rat brain the noradrenergic system works on a significantly higher activity level in the HP strain than in the LP strain, and the sensitivity of the catecholaminergic machinery in the brain is significantly more sensitive toward a synthetic enhancer substance in the HP strain than in the LP strain.

Collating the result of the longevity study (25) with this specially designed experiment (33), we can say that the HP rats have a better brain engine than the LP rats.

The Natural Death Situation in the Light of the Enhancer Regulation and an Experimental Model to Mimick This Situation in Young Rats

Natural death sets in when the catecholaminergic system's ability to activate the telencephalon sinks below a critical threshold and at an emergency incident, when a high level of activation is needed to survive the tribulation and the cortical neurons cannot be activated any further to the required level. This would explain why, for example, a common infection or a broken leg, which with full-capacity working catecholaminergic machinery in place is an easily surmountable challenge, may cause death in old age (see 2 for review).

The age-related decline of the brain engine makes it unavoidable that with the passing of time every living being arrives once to a natural death situation. But, because the essence of this situation is the relative weakness of the brain engine, and we have in a random rat population higher- and lower-performing individuals, we can create experimental circumstances that mimick a natural death situation to which low-performing young rats, otherwise healthy animals full of vigor, fall victim.

In our effort to find for the rat the most favorable conditions for the acquisition of the glass-cylinder–seeking drive, we analyzed in detail the kinetics of the escape of rats from a hot plate at different temperatures (for review see 1, Chapter III, pp. 43–53). The essence of the method (see 1, Fig. 6) was a copper hot plate (180 × 180 mm) the temperature of which could be regulated with an accuracy of ±0.2°C. The metal surface was heated to the desired temperature and a glass cylinder, 30-cm high, with bottom and top diameters of 16 and 12 cm, respectively, was placed at the top of it. The cylinder, opened on bottom and top, had no side openings. The experiment was performed on female rats weighing 120–150 g. The animals were dropped onto the heated metal plate, through the upper opening of the cylinder. The time elapsing between their fall and subsequent jump onto the cylinder's top was measured. Ten such tests were usually performed at 30-s intervals. If the animal had not jumped out of the cylinder in 4 h in any of the tests, no further measurements were made and the 4-h time was referred to as maximum value.

There can be little doubt that the chain of events in the brain of the rat that successfully escaped from the hot plate was the following. The heat/pain stimulation enhanced the activity of the catecholaminergic system, and, in proportion, the cortical neurons started to work on a higher activity level, allowing the acquisition of those chains of extinguishable conditioned reflexes that enabled finally the escape from the hot plate. Rats with inadequately activated brain engine are in danger.

At 40°C, the animals stayed in the cylinder throughout the whole period of 240 min, thus this heat stimulus was subliminal for eliciting the escape reaction. The lowest temperature that elicited jumping onto the rim of the upper opening of the cylinder was 45°C. The time needed for escape at this temperature varied from 25 to 164 min in a group of naive rats (n = 10) (see 1, Table XIII). This is a harmless situation, and the experiment did not change the health condition of any of the rats.

Raising the temperature of the hot plate to 50°C changed the situation significantly. This not too intensive heat/pain stimulus is an insidous one that becomes life-threatening for a low-performing animal. At this temperature, of a group of 10 naive rats, 6 animals escaped within 2–13 min and remained healthy. However, 4 rats were unable to cope with the situation; 3 of them died and the fourth became seriously ill. Table III shows the details of this series of experiments.

Testing the escape reaction of a group of 10 rats from a hot plate heated to 55°C yielded a much more

Table III. Escape of Rats from a Hot Plate at 50°C. Optimal Temperature to Mimick a "Natural Death" Situation for Low Performing Rats

	Jumping reactions in round minutes on										
Serial number	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Note
	day of experiment										
1	2	1	2	1	1	1	1	1	1	1	
2	2	1	2	2	2	1	1	1	1	1	
3	34	1	2	3	12	11	3	3	1	1	Ill
4	10	1	1	4	7	1	1	1	1	1	
5	13	7	4	8	5	7	2	1	1	1	
6	4	1	3	3	13	1	1	1	1	1	
7	8	7	4	2	2	8	2	1	2	2	Ill
8	34	14	32	2	22	6	6	2	—	—	Ill, died
9	49	38	—	—	—	—	—	—	—	—	Ill, died
10	63	—	—	—	—	—	—	—	—	—	Ill, died
Mean round minutes	22	8	6	3	8	5	2	1	1	1	

Note: Mean rectal temperature on 1st day

immediately after 1st measurement	38.8 ± 0.9
immediately after 10th measurement	39.7 ± 1.0
30′ after 10th measurement	37.1 ± 0.4

See 1, Chapter III for methodological details

favorable result. Nine rats of the group escaped at between 1 and 6 min and remained healthy. One animal needed 14 min to escape and later became seriously ill (see 1, Table XV).

The heat/pain stimulus elicited by a hot plate at 60°C was too strong and confused some of the animals; of a group of 10 animals, 3 died and 1 became ill (see 1, Table XVI). Nevertheless, for producing glass-cylinder–seeking rats we used this temperature because it proved to be the most efficient for this purpose.

The success of the escape of naive rats from the hot plate depends primarily from the efficiency of their catecholaminergic brain engine. This was shown in a series of experiments performed on rats pretreated for 4 weeks, once daily, with 0.1 mg/kg reserpine. None of a group of 10 reserpine-treated rats escaped from a hot plate heated to 55°C, they all died. However, 7 out of 10 reserpine-treated rats safely escaped when the temperature of the hot plate was raised to 60°C (see 1, Table XIX).

All in all, the data substantially support the view that natural death sets in when the catecholaminergic system's ability to activate the telencephalon sinks, for whatever reason, below a critical threshold.

Enhancer Receptors

The finding that (−)-BPAP exerted its enhancer effect in *in vitro* experiments on noradrenergic, dopaminergic, serotonergic and hippocampal neurons in the low nanomolar concentration range (12) clearly indicated that this effect was elicited via the stimulation of a highly specific enhancer receptor.

Convincing indirect proof for specific enhancer receptors in the dopaminergic system was already furnished by a recent study (34). 1-(2-Benzofuryl)-2-(3,3,3-trifluoropropyl) aminopentane HCl (3-F-BPAP) a close structural analogue of BPAP with weak enhancer activity was synthesized with the expectation that the simultaneous administration of this analogue with (−)-BPAP will significantly antagonize the enhancer effect of the latter, proving that they act on the same receptor. The low specific activity of 3-F-BPAP was demonstrated in the rat in the shuttle box.

The subcutaneous administration of 1 mg/kg tetrabenazine once daily for 5 days that depletes the catecholamine stores in the brain, significantly inhibiting the acquisition of a two-way avoidance reflex in the shuttle box. This effect can be significantly antagonized by enhancer substances. The effect of (−)-BPAP was measured in eight different doses from 0.05 to 10 mg/kg. Even the lowest dose significantly antagonized tetrabenazine-induced inhibition of learning. In contrast, 3-F-BPAP was ineffective in five different doses, ranging from 0.25 to 5.0 mg/kg (34, Table 3).

The concurrent administration of 1 mg/kg 3-F-BPAP with 0.1 mg/kg (−)-BPAP significantly inhibited

the enhancer effect of (−)-BPAP but 1 mg/kg 3-F-BPAP did not influence the enhancer effect of 1 mg/kg (−)-BPAP (34, Fig. 2). This is clear indication that the compounds bind to the same receptor to which (−)-BPAP has a much higher affinity than 3-F-BPAP.

(−)-Deprenyl, at present the only enhancer drug in general use, though being substantially less potent in the shuttle box than (−)-BPAP, significantly antagonized the learning deficit caused by tetrabenazine. We studied the effect of 1 and 5 mg/kg (−)-deprenyl in different combinations with 1 and 5 mg/kg 3-F-BPAP and found that 3-F-BPAP left the enhancer effect of (−)-deprenyl unchanged (34, Fig. 2). Furthermore, 3-F-BPAP did not influence the enhancer effect of (−)-PPAP, a (−)-deprenyl analogue free of MAO-B inhibitory potency (34, Fig. 4).

The data clearly show that the molecular mechanism through which the PEA-derived substances, (−)-deprenyl and (−)-PPAP, exert their enhancer effect *in vivo,* is not identical with the one through the stimulation of which the tryptamine-derived substance, (−)-BPAP, acts. This is in harmony with the finding that in contrast to (−)-BPAP, (−)-deprenyl did not exert an enhancer effect on the serotonergic neurons (12). That (−)-BPAP is enhancing the activity of the catecholaminergic and serotonergic neurons in the rat brain via the stimulation of a highly specific enhancer receptor is strongly supported by the finding that the compound did not show a significant binding capacity to any of the receptors known to play a role in the function of the catecholaminergic and serotonergic neurons in the brain (see 12, Table 4).

The characteristic enhancer effect of (−)-BPAP, as shown for example in Fig. 9, presenting one bell-shaped dose/concentration effect curve in the low nanomolar range and another one at a higher micromolar range (12,14) indicate the existence of two types of specific (−)-BPAP-sensitive enhancer receptors in the brain: a high-affinity binding site stimulated in the nanomolar range and a low-affinity binding site stimulated in higher macromolar range. The recent identification of a family of G-protein–coupled receptors (trace-amine receptors) in the mammalian brain specifically stimulated by the endogenous enhancer substances PEA and tryptamine (35) strongly suggests that the authors located a family of enhancer receptors.

The already realized obvious difference between the binding of (−)-deprenyl and (−)-BPAP (34) argues for the existence of various types of enhancer receptors in the brain. Remarkably, Borowsky et al. (35) found that more than one member of the newly identified family of mammalian G-protein–coupled receptors were activated by PEA and tryptamine.

Studies with (−)-BPAP, the most potent and selective enhancer substance that is presently the best experimental tool for the analysis of functionally important enhancer receptors, are at the very beginning. Nevertheless, two studies were already published showing that (−)-BPAP has remarkable binding capacity also to other receptors than those responsible for the specific behavioral effects of the enhancer substances. Hamabe et al. (28) demonstrated that high concentrations of (−)-BPAP displaced the binding of [^{3}H]-(+)-pentazocine to sigma receptors in the synaptic membranes from rat cerebral cortex. Thereafter, Rashid et al. (36) has found that (−)-BPAP binds to metabotropic sigma receptors in peripheral nociceptor endings. The sigma agonist-induced nociception was found to be due to the release of substance P from nociceptor endings through activation of $G\alpha_{i1}$ and phospholipase C (37). A number of studies indicated that sigma agonists stimulate heterometric G-proteins (38–40). The nociceptive flexor responses in mice induced by both (+)-pentazocine and (−)-BPAP were blocked by sigma receptor antagonist BD 1063. In radio-ligand binding assay, [^{3}H]-(+)-pentazocine showed a saturable specific binding in membrane preparation from mouse liver, and this specific [^{3}H]-(+)-pentazocine binding was inhibited by (−)-BPAP, as well as by (+)-pentazocine and BD 1063 (36).

It is obvious that the binding of (−)-BPAP to the sigma receptors is unrelated to the behavioral effect of the compound. Research in progress is now devoted to clarifying the real nature of the enhancer receptors through the stimulation of which low nanomolar concentrations of (−)-BPAP exerted their specific enhancer effect on the mesencephalic neurons.

The endogenous ligands to the specific enhancer receptors is another open question that remains to be answered. Because of the high potency of (−)-BPAP in comparison to the already identified endogenous enhancer substances PEA and tryptamine, it is reasonable to assume that unknown, much more potent endogenous ligand(s) to the enhancer receptors operate in the mesencephalon and could be responsible, for example, for the significantly enhanced orienting-searching reflex activity in goal-seeking behavior. Research is now in progress to test the validity of this assumption.

THE THERAPEUTIC VALUE OF SYNTHETIC ENHANCER SUBSTANCES IN AGE-RELATED NEUROLOGICAL DISEASES AND DEPRESSION

Synthetic Enhancer Substances in Depression

(−)-Deprenyl was found to be a potent antidepressant (see 3 for review).

Making use of the promising antidepressant effect of the tryptamine-derived newly developed, highly potent and selective enhancer substance will be a challenge because (−)-BPAP is about 130 times more potent than (−)-deprenyl in rats for antagonizing tetrabenazine-induced depression in the shuttle box. A recent study corroborated the catecholaminergic, mainly dopaminergic activity enhancer effect of (−)-BPAP. It potentiated locomotor activity in nonhabituated rats and reversed reserpine-induced hypolocomotion; these effects were attenuated by the dopamine D_1 receptor antagonist (SCH 223390). In addition, the administration of (−)-BPAP increased ipsilateral turning in unilaterally 6-OH-dopamine lesion rats, implying presynaptic activation of nigrostriatal dopaminergic terminals by (−)-BPAP (41). All these effects are in harmony with the expectation of the clinical benefit of (−)-BPAP in depression.

Synthetic Enhancer Substances in Parkinson's Disease

Since the beneficial effect of (−)-deprenyl (Selegiline) was first demonstrated in Parkinson's disease by Birkmayer et al. in 1977 (42), hundreds of clinical papers confirmed its effectiveness. (−)-Deprenyl is used now worldwide as a drug that slows the progress of early Parkinson's disease (see 3 for review).

The beneficial effect of (−)-deprenyl is primarily due to its enhancer effect (see 9 for review). With the development of (−)-BPAP, a selective and much more potent enhancer substance than (−)-deprenyl, there are several promising opportunities in the treatment of Parkinson's disease. We may slow the progress of the disease and shift the time until levodopa is needed in *de novo* patients with Parkinson's disease with (−)-BPAP and accomplish treatment later, when levodopa is already needed, with a carefully adjusted dose of (−)-deprenyl, to make safe use of its levodopa-sparing effect because of the MAO-B inhibitory potency of the drug.

There is experimental evidence that the levodopa-sparing effect of (−)-deprenyl is exclusively related to the inhibition of MAO-B. The MAO-A/MAO-B ratio is 1:1 in the rat striatum and 1:9 in marmosets. Accordingly, repetitive administration of 0.1 mg/kg (−)-deprenyl did not cause any increase in extracellular dopamine concentration in the striatum of rats after levodopa/carbidopa injection, whereas the same treatment led to a sevenfold increase in the extracellular concentration of dopamine in the striatum of marmosets (43). Nevertheless, a recent study showed that (−)-BPAP, the 130-times more potent new enhancer substance than (−)-deprenyl, though free of MAO-B inhibitory potency, exerted a significant levodopa-sparing effect in rat experiments (44).

Synthetic Enhancer Substances in Alzheimer's Disease

The development of Alzheimer's disease, the progressive neurodegenerative illness that is the most relevant form of late-life mental failure in humans is, according to present views, closely related to the production of β-amyloid$_{1–42}$ from its precursor, β-APP, by sequential proteolytic clavage. β-Amyloid$_{1–42}$, a neurotoxic component of the intraneuronal senile plaques, is thought to be the key molecule in the pathology of Alzheimer's disease. Because β-amyloid$_{25–35}$ is more rapidly toxic and causes more oxidative damage than its parent compound, β-amyloid$_{1–42}$, this smaller peptide is now preferentially used to cause oxidative damage to cultured neurons (see 45 for review).

On cultured hippocampal neurons (−)-BPAP antagonized the neurotoxic effect of β-amyloid$_{25–35}$ in the low nanomolar concentration range with a peak effect at 10^{-14} M concentration (12, Fig. 5). In a recent study the neuroprotective effect of (−)-deprenyl and (−)-BPAP was studied on β-amyloid$_{25–35}$–induced cell death using cultured cortical neurons from chick embryos. (−)-BPAP significantly antagonized the toxic effect of β-amyloid$_{25–35}$ in the low nanomolar concentration range with a peak effect at 10^{-14} M concentration (Fig. 11). In this Alzheimer model test (−)-deprenyl showed some neuroprotective effect in 10^{-10} M concentration, but was unequivocally much less potent than (−)-BPAP (46).

It is in accordance with the experimental data that (−)-deprenyl exerts a beneficial effect in Alzheimer's disease (see 3 for review), and it was concluded that in patients with moderately severe impairment from Alzheimer's disease, treatment with (−)-deprenyl slows the progression of the disease (47). Because (−)-BPAP

exerts a much more potent neuroprotective effect in model experiments than (−)-deprenyl, we may reasonably expect that this compound will be substantially more potent in slowing the progress of Alzheimer's disease than (−)-deprenyl.

SUMMARY AND CONCLUSION

Drive, the inner force that activates the mammalian organism to surmount every obstacle to reach a goal, even if life is in the balance, is rooted in the existence of enhancer-sensitive neurons in the mesencephalon and telencephalon that are ready to increase their activity with lightning speed in response to endogenous enhancer substances. The mesencephalic enhancer regulation is primarily responsible for reaching the limited number of indispensable goals needed for the survival of the individual and the species (inner drives), and the telencephalic enhancer regulation enables to reach an unlimited number of dispensable goals (acquired drives).

The catecholaminergic and serotonergic neurons in the brain of rats were primarily used to study the characteristics of the mesencephalic enhancer regulation. Experiments were performed *in vivo,* on isolated discrete brain regions in an organ bath, and on isolated brain cells in culture. Already identified endogenous enhancer substances, PEA and tryptamine, and their synthetic derivatives, (−)-deprenyl (selegiline) and (−)-BPAP, were used as experimental tools.

(−)-BPAP, the most selective and most potent enhancer substance, significantly enhanced the activity of the catecholaminergic and serotonergic neurons in the brain 30 min after acute injection of 0.1 μg/kg SC. (−)-BPAP exerted its enhancer effect on isolated discrete brain regions or on isolated mesencephalic neurons in culture in a nanomolar concentration range with a peak at 10^{-14} M concentration. This effect is characterized by a typical bell-shaped dose/effect curve that allows a new interpretation for the well-known substantial individual variation in learning performance.

The mesencephalic enhancer regulation works during the uphill period of life, from weaning until sexual maturity, on a significantly higher activity level. Sexual hormones dampen the mesencephalic enhancer regulation, and bring it back to the preweaning level, thereby terminating the uphill period. This is the prelude for the postdevelopmental phase of life. The slow age-related decline of the mesencephalic enhancer regulation is the essence of the brain aging process from which there is no escape until natural death.

Enhancer substances that keep the mesencephalic enhancer-sensitive neurons on a higher activity level slow the age-related deterioration of the mammalian brain. Maintenance of rats on (−)-deprenyl during postdevelopmental longevity slows the age-related decline of sexual and learning performance and prolongs life significantly. Patients with early Parkinson's disease, who are maintained on (−)-deprenyl, need levodopa significantly later than their placebo-treated peers, and they live significantly longer when on levodopa plus (−)-deprenyl than patients on levodopa alone. In patients with moderately severe impairment from Alzheimer's disease treatment with (−)-deprenyl slows the progression of the disease.

(−)-BPAP is an especially promising prophylactic antiaging compound that may provide the opportunity to shift the functional constellation of the brain during postdevelopmental longevity toward the one characteristic to the uphill period of life. According to the available experimental and clinical data, it is reasonable to expect that daily administration of an enhancer drug [e.g., (−)-deprenyl 1 mg or (−)-BPAP) 0.1 mg] from sexual maturity until death will improve the quality of life in the latter decades, shift the time of natural death, decrease the precipitation of age-related depression, and reduce the prevalence of Parkinson's disease and Alzheimer's disease.

The characteristics of the telencephalic enhancer regulation was studied in rats that acquired the glass-cylinder–seeking drive, and on cultured cortical cells of rats (docile animal) and chicken (an animal unable to acquire an unnatural drive). The experiments led to the conclusion that in contrast to the mesencephalic neurons, born in all species with a fixed enhancer regulation, the cortical neurons posses a fixed enhancer regulation only in species unable to acquire an unnatural drive. Cortical neurons of docile animals, capable of acquiring drives, are born with the potential to establish by the aid of proper training their specific enhancer regulation. This mechanism is the basis of the acquired drives. The appearance of species with the ability to acquired drives for unnatural goals was probably the last crucially important leap in the development of brain organization. In the animal kingdom this development reached its functionally most sophisticated level in the group of anthropoid apes, but the mechanism reached its level of perfection only in *Homo sapiens*.

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