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Review

From Deficiency to Enhancement: β-Phenylethylamine, the Endogenous Precursor of Catecholaminergic Psychostimulants

Comparative Pharmacology, Clinical Associations, Patterns of Use, and Role as an Endogenous Catecholaminergic Modulator

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Abstract

Humans consistently seek states of heightened focus, motivation, energy, and enhanced cognitive performance and positive affect. Three catecholaminergic agents predominate in this pursuit: cocaine, amphetamines (both licit and illicit), and modafinil. Each is effective, and each carries a distinct cost, including illegality, prescription controls, or pharmacologically determined risks of adverse effects and dependence. β-Phenylethylamine (PEA), the endogenous, unsubstituted parent phenethylamine and the metabolic and structural progenitor of amphetamine, engages the same catecholaminergic substrate through a distinct, firing-coupled, self-limiting mechanism. However, its physiological effects are curtailed by rapid catabolism via monoamine oxidase B (MAO-B). This paper compares the four agents in terms of molecular mechanisms, pharmacokinetics, neurocircuitry and behavioral pharmacology, sensory and perceptual effects, human subjective effects, abuse liability, and current epidemiological patterns of use. It then develops the pharmacological rationale for selective MAO-B protection as a means of converting PEA from a transient endogenous signal into a sustained, functionally meaningful one, and examines the safety parameters—primarily MAO-B selectivity and potential drug interactions—that govern such a strategy. The analysis identifies a persistent gap between the substantial and growing demand for catecholaminergic enhancement and the near absence of a safe, legal, endogenous means of meeting it.

Keywords: β-phenylethylamine; trace amines; TAAR1; dopamine; monoamine oxidase B; psychostimulants; cognitive enhancement; abuse liability

1. Introduction

The desire for sharper focus, sustained energy, greater motivation, and an improved mood is universal and enduring, and pharmacological means have been used to address it across cultures. In contemporary settings, three agents predominate: cocaine; amphetamines, in both licit (prescription) and illicit forms; and the wakefulness-promoting agent modafinil. All three are effective because they converge on the same neurochemical substrate—the augmentation of synaptic catecholaminergic tone, principally dopaminergic. All three also carry structural costs inseparable from their pharmacology: two are largely illegal, while the third is prescription-controlled, and each entails adverse effects and, to varying degrees, a risk of dependence arising directly from its mechanism and kinetics.

β-Phenylethylamine (PEA) occupies a distinctive position in this landscape. It is an endogenous trace amine and the unsubstituted parent of the phenethylamine class [1], as well as the direct structural and metabolic progenitor of amphetamine, which is simply PEA bearing a single α-methyl group. PEA engages the catecholaminergic system through a mechanism distinct from the releasers and reuptake inhibitors that characterize the comparator drugs, and it does so in a self-limiting,

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physiological manner. Its functional expression, however, is constrained by its near-immediate catabolism by monoamine oxidase B (MAO-B). This paper compares PEA with cocaine, amphetamine, and modafinil in terms of mechanism, pharmacokinetics, behavior, sensation, and subjective effects; situates these four agents within current patterns of use; and develops the pharmacological rationale for an endogenous, enzymatically protected catecholaminergic modulator as a category distinct from the drugs currently used to meet this demand.

2. Comparative Molecular Pharmacology

2.1. β-Phenylethylamine

PEA is synthesized from L-phenylalanine by aromatic L-amino acid decarboxylase (AADC) and maintained at low-nanomolar concentrations in the central nervous system through rapid turnover. Its principal receptor target is trace amine-associated receptor 1 (TAAR1) [2–4], a predominantly intracellular, Gαs-coupled receptor. TAAR1 activation increases cAMP/PKA signaling and, through functional coupling with the dopamine transporter (DAT) and Kir3/D2-autoreceptor signaling, modulates dopaminergic tone and promotes DAT phosphorylation, internalization, and reverse transport [5]. PEA also acts as a substrate-type releaser at DAT and NET, eliciting carrier-mediated dopamine and norepinephrine efflux. In accordance with Knoll's catecholaminergic-activity-enhancer (CAE) concept, it potentiates impulse-propagation-coupled exocytotic release independently of its releaser action [6]. Catabolism occurs predominantly via MAO-B and, secondarily, via MAO-A, forming phenylacetic acid. This results in a central half-life on the order of minutes and negligible systemic accumulation in the absence of MAO-B inhibition [7].

2.2. Cocaine

Cocaine competitively inhibits the plasma membrane monoamine transporters DAT, NET, and SERT, thereby blocking reuptake and increasing synaptic dopamine, norepinephrine, and serotonin levels. Its reinforcing efficacy is associated with DAT occupancy and, according to the rate hypothesis, with the speed of transporter blockade enabled by rapid entry into the central nervous system [8]. In addition to its monoaminergic effects, cocaine also produces use-dependent blockade of voltage-gated sodium channels, resulting in local anesthetic and membrane-stabilizing effects—a property unique among the agents considered here.

2.3. Amphetamine

Amphetamine is a substrate-type releaser that is transported into the terminal via DAT/NET. It triggers the reverse transport of cytosolic monoamines, disrupts vesicular sequestration through VMAT2, and weakly inhibits MAO. Together, these effects drive substantial, firing-independent elevations in dopamine and norepinephrine [9,10]. Amphetamine is also a TAAR1 agonist. Its action is enantioselective: the d-isomer has a greater dopaminergic effect, whereas the l-isomer has a relatively greater noradrenergic effect. The α-methyl substituent, which distinguishes amphetamine from PEA, confers resistance to MAO degradation and oral bioavailability, providing the molecular basis for its prolonged and abuse-prone effects.

2.4. Modafinil

Modafinil is an atypical wakefulness-promoting agent. It binds to DAT and inhibits dopamine reuptake with low affinity but functional selectivity; its arousal effects are DAT-dependent and produce a modest increase in dopamine, preferentially in the nucleus accumbens and prefrontal cortex. In parallel, it recruits wake-promoting circuitry—including orexinergic and histaminergic activation, increased cortical and thalamic noradrenergic and glutamatergic tone, decreased GABA, and enhanced electrotonic thalamocortical coupling—thereby producing arousal with comparatively low mesolimbic reinforcing salience [11,12].

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Table 1. Mechanism at a glance.

Agent	Primary action	TAAR 1	Other targets	Onset	Duration
PEA	Substrate release + firing-coupled enhancement (CAE)	Agonist	—	Fast	Minutes
Cocaine	Reuptake inhibition (DAT/NET/SERT)	—	Na^+-channel block	Fast	~1 h
Amphetamine	Substrate release (transporter reversal)	Agonist	VMAT2; weak MAOI	Fast	~9–14 h
Modafinil	Weak DAT reuptake inhibition	—	Orexin/histamine/NE/glutamate↑, GABA↓	Moderate	~12–15 h

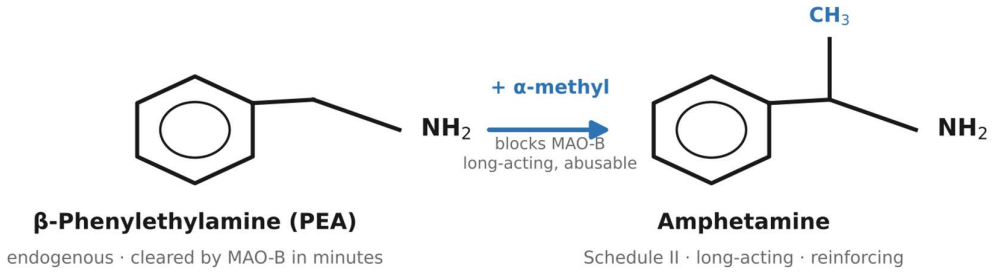

Figure 1. Structural lineage: PEA is the parent of the amphetamines. α-Methylation of the phenethylamine scaffold yields amphetamine and confers resistance to MAO-B degradation — the single change that turns the endogenous parent into a long-acting, scheduled drug.

3. Pharmacokinetics and Disposition

Agent	Principal target(s)	Metabolism	$t_{1/2}$ (approx.)
PEA	TAAR1 agonist; DAT/NET substrate-releaser; CAE	MAO-B (› MAO-A) → phenylacetic acid	~minutes
Cocaine	DAT/SERT/NET reuptake inhibitor; Na^+-channel blocker	Plasma/hepatic esterases	~0.7–1.5 h
Amphetamine	DAT/NET substrate-releaser; VMAT2; TAAR1; weak MAOI	Hepatic (CYP2D6); renal, pH-dependent	~9–14 h
Modafinil	Weak selective DAT inhibitor; orexin/histamine/NE/glutamate↑, GABA↓	Hepatic (CYP3A4)	~12–15 h

4. Neurocircuitry and Behavioral Pharmacology

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Reinforcement is mediated by the mesolimbic dopamine pathway, which projects from the ventral tegmental area to the nucleus accumbens. Cognitive and arousal enhancement are mediated by mesocortical dopaminergic and noradrenergic inputs to the prefrontal cortex, which exhibit an inverted-U dose–response relationship through D1 and α_2A receptors.

Cocaine and amphetamine produce robust conditioned place preference, intravenous self-administration, and locomotor sensitization, consistent with high reinforcing efficacy and dependence liability [8,9]. Modafinil promotes wakefulness and enhances sustained attention and working memory, while producing weak locomotor sensitization and lower self-administration than cocaine [12]. PEA elicits transient, dose-dependent locomotor activation in rodents [13], but its reinforcing profile is weak and short-lived because of rapid MAO-B catabolism. Co-administration of an MAO-B inhibitor markedly potentiates and prolongs its behavioral effects—an empirical observation central to the subsequent sections.

5. Sensory, Autonomic, and Perceptual Effects

Cocaine and amphetamine induce sympathomimetic autonomic activation—including mydriasis, tachycardia, hypertension, and diaphoresis—alongside heightened arousal and vigilance. Sustained striatal and mesolimbic hyperdopaminergia during high-dose or chronic exposure can precipitate stimulant psychosis, characterized by paranoia and auditory and tactile hallucinations (formication). Cocaine also causes somatosensory alterations, such as mucosal anesthesia, through sodium-channel blockade. Modafinil produces minimal autonomic or perceptual disturbance, with headache being the most common sensory complaint [12]. At physiological exposure levels, PEA causes negligible perceptual alteration; effects observed under MAO-inhibited or supraphysiological conditions reflect amplified catecholaminergic signaling rather than an intrinsic hallucinogenic action.

6. Human Subjective Effects and Abuse Liability

Subjective effects are quantified using validated instruments, including the Addiction Research Center Inventory (ARCI), the Drug Effects Questionnaire (DEQ: “feel,” “like,” “want more”), and visual analog scales. In preclinical research, the drug-discrimination paradigm is used to operationalize the interoceptive stimulus. Cocaine and amphetamine produce pronounced positive subjective effects, including euphoria, stimulation, and increased drug liking and wanting, and share an amphetamine-like discriminative cue, with abuse liability increasing with dose. Modafinil has a comparatively subdued subjective-effects profile and low drug-liking ratings; at high doses, it can partially substitute for an amphetamine discriminative stimulus while producing blunted euphoria, consistent with its Schedule IV status [12]. PEA substitutes for amphetamine in drug-discrimination assays and produces transient positive affect in humans [14]. However, its rapid MAO-B catabolism limits the duration of the interoceptive and reinforcing signal, providing a pharmacological basis for its minimal abuse liability.

Table 2. Comparative risk and abuse-liability profile.

Agent	DEA schedule	Dependence liability	Key adverse effects	Status
PEA	Unscheduled	Negligible	Minimal at functional exposure	Endogenous; food / supplement
Cocaine	Schedule II	High	Cardiotoxicity, psychosis, addiction	Illicit (medical use rare)

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Amphetamine	Schedule II	High	Cardiovascular load, dependence, psychosis	Prescription (e.g., Adderall)
Modafinil	Schedule IV	Low–moderate	Headache; rare serious rash; some dependence potential	Prescription

7. Patterns and Prevalence of Use

Demand for catecholaminergic enhancement is substantial and growing for several agents. In the United States, the National Survey on Drug Use and Health (ages 12 and older, past year) estimated that 4.3 million people used cocaine (1.5%), 2.4 million used methamphetamine (0.8%), and 3.9 million misused prescription stimulants (1.4%) [15]. Licit prescription use is greater still: approximately 16.5 million patients received prescription stimulants, accounting for approximately 80.8 million prescriptions annually, of which 41.3 million were amphetamine/dextroamphetamine products [16]. Among adult users, roughly one quarter report nonmedical use, and about nine percent meet the criteria for a prescription stimulant use disorder. Globally, the United Nations Office on Drugs and Crime estimated that 23.5 million people used cocaine and approximately 30 million used amphetamines in 2022, out of a total of 331 million people who used any drug [17].

Against these figures, modafinil is used by a far smaller population—through prescribing for narcolepsy, obstructive sleep apnea, and shift-work disorder, as well as off-label cognitive-enhancement use documented in surveys but unquantified at the population level [12]. PEA is effectively absent from population data, circulating only as a niche nootropic supplement and an endogenous dietary constituent. The distribution is therefore highly asymmetric: the states these agents produce are sought by tens of millions through channels that are illegal, prescription-gated, or pharmacologically hazardous, while the one endogenous agent capable of engaging the same substrate sees negligible deliberate use.

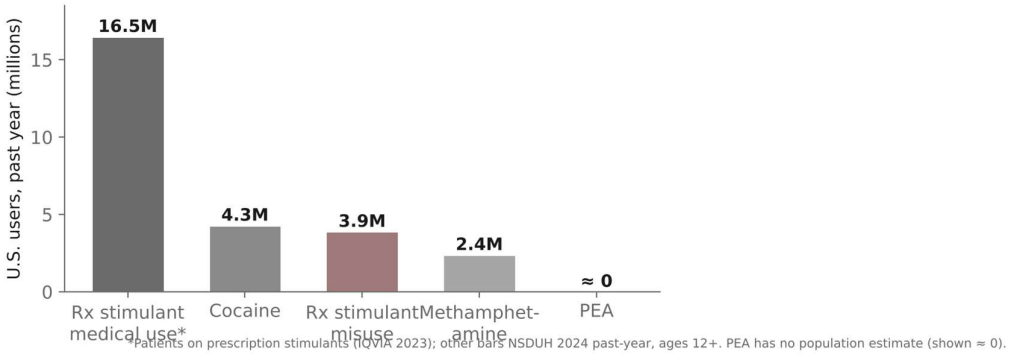

Figure 2. Scale of use—the demand for catecholaminergic states vs. PEA's footprint. The states these agents produce are pursued by tens of millions through illegal or prescription channels, while PEA has negligible deliberate population use.

8. Human Evidence for PEA

8.1. The Phenylethylamine Hypothesis and the Sabelli Program

Direct evidence in humans for a role of PEA in affect dates to Sabelli and Mosnaim, whose 1974 phenylethylamine hypothesis of affective behavior [18] proposed that reduced central PEA activity contributes to depressive states. Over the subsequent two decades, Sabelli and colleagues assembled supporting clinical data: urinary phenylacetic acid (PAA), the principal PEA metabolite and an index of PEA turnover, was reported to be reduced in major depression and was proposed as a candidate diagnostic marker [14].

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The hypothesis was also examined through measurements of urinary and blood PAA and supplementation with phenylalanine, the PEA precursor [19]. This research program culminated in a direct therapeutic test. Because oral PEA is catabolized within minutes, Sabelli administered it with a low dose of the selective MAO-B inhibitor selegiline (10 mg/day; oral PEA 10–60 mg/day). Approximately 60% of depressed patients responded. In a follow-up assessment of fourteen responders at 20–50 weeks, the effect was maintained in twelve (≈86%), without dose escalation or tolerance [20]—a durability distinct from that of conventional psychostimulants and the central human proof of concept for the enzymatic-protection strategy developed in Section 10.

8.2. Extension by Later Investigators

Subsequent research extended this association across several domains. In exercise physiology, thirty minutes of treadmill exercise at 70% of heart-rate reserve increased 24-hour urinary PAA by 77% in healthy men, implicating endogenous PEA in exercise-related mood elevation [21]. In attention-deficit phenotypes, reduced PEA levels were reported in affected adults [22] and children [23]. Urinary PEA increased following methylphenidate administration, and higher levels were associated with symptom improvement [24]; PEA was later catalogued among candidate ADHD biomarkers [25]. Mechanistic studies provided a receptor-based explanation for these observations: PEA modulates monoamine-transporter function through TAAR1 [5], and TAAR1 agonists exhibit antidepressant- and antipsychotic-like activity in rodent and primate models [26]. More recent rodent research indicates that PEA attenuates chronic corticosterone-induced depressive-like behavior through hippocampal BDNF signaling [27]. Human and preclinical findings further support a modulatory role: urinary PEA increases after acute stress [28], and in vivo studies confirm PEA-evoked dopamine and serotonin release [29].

Table 3. Key human and genetic evidence for PEA.

Study	Design	Subjects	Finding
Sabelli et al. 1996	Open follow-up	14 responders	PEA + selegiline; response maintained in 12/14 at 20–50 wks, no tolerance
Sabelli et al. 1986	Clinical	Depressed patients	Reduced PAA; phenylalanine / PEA supplementation examined
Szabo et al. 2001	Controlled	20 healthy men	30-min exercise raised 24-h urinary PAA by 77%
Kusaga et al. 2002	Case–control	ADHD children	Urinary PEA low; rose with methylphenidate and tracked improvement
Grimsby et al. 1997	Transgenic	MAO-B–deficient mice	Elevated brain PEA — confirms MAO-B governs PEA levels

8.3. Skeptical and Null Findings

The literature is not uniform, and a comprehensive account must include dissenting findings. Sandler and colleagues [30] found deficient tyramine and octopamine metabolites in depression but no significant change in PEA, while DeLisi and colleagues [31] reported that urinary PEA neither correlated with PAA excretion nor tracked depressive symptoms. These null results, together with the inherent difficulty of using peripheral metabolites to index a trace amine with a half-life measured in minutes, temper the strength of the clinical claim. Notably, no large, modern controlled trial of PEA itself has been conducted since the Sabelli program, despite independent validation of the underlying mechanism—TAAR1 signaling and enhancer regulation. This combination of an early human signal, a validated mechanism, and the absence of modern clinical development is revisited in the Discussion.

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8.4. Knoll's Enhancer Datasets

The most extensive mechanistic dataset is that of Knoll, who characterized PEA, together with tryptamine, as a natural catecholaminergic and serotonergic activity enhancer and formalized the enhancer-regulation framework [6]. In rodent models, low, sub-releasing doses of PEA and the PEA-derived enhancers selegiline and (−)-BPAP potentiate the impulse-coupled release of catecholamines and serotonin, exhibiting a characteristic bell-shaped dose–response relationship that differs from the releasing action observed at higher doses. Knoll reported that high-performing animals are more sensitive to catecholaminergic activity-enhancer compounds than their low-performing counterparts, and that chronic administration of the enhancer selegiline prolonged lifespan and preserved performance in rats [32]—findings he interpreted as evidence that enhancer regulation governs the vitality of the catecholaminergic system throughout the lifespan.

9. PEA Deficiency in Catecholaminergic Disorders

PEA's clinical associations extend beyond mood: reduced PEA levels or turnover have been reported across a range of disorders characterized by diminished catecholaminergic activity, consistent with its role as a physiological modulator of that system rather than as a simple stimulant.

9.1. Disorders of PEA Deficiency

Reduced PEA levels or turnover have been reported across disorders characterized by diminished catecholaminergic drive. In addition to major depression (Section 8.1), urinary PEA levels are decreased in children with ADHD and autistic disorder and increase with methylphenidate treatment [23]. Cerebrospinal fluid PEA levels are reduced in Parkinson's disease [33], consistent with nigrostriatal dopaminergic degeneration. Alzheimer's disease and age-related decline are also associated with catecholaminergic underfunction in the mesolimbic-cortical and nigrostriatal systems. The shared phenotype—anergia, reduced motivation, and attentional and hedonic impairment—corresponds to the functions normally supported by PEA and defines deficiency states in which restoration may be of interest.

Table 4. Reduced PEA across catecholaminergic-deficit disorders.

Disorder	PEA / PAA	Specimen	Reference
Major depression	Decreased	Urine / blood	Sabelli (1974–1996)
ADHD / autism	Decreased	Urine	Baker 1991; Kusaga 2002
Parkinson's disease	Decreased	CSF	Shoji 1997

9.2. A Regulator of Catecholaminergic Drive

Across these conditions, the consistent association between reduced PEA and diminished drive, attention, and motivation supports a role for PEA as a physiological modulator of catecholaminergic tone and identifies deficiency states in which restoring that tone is rational. Because PEA acts in concert with the neuron's own firing and is subject to receptor-level autoregulation, the appropriate strategy is selective, titratable support of endogenous PEA rather than unopposed enzyme blockade (Section 10).

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Figure 3. From deficiency toward functional enhancement. PEA-deficiency states on the left; restoring catecholaminergic drive is proposed to move function toward the enhancement end.

10. MAO-B Protection and the Functional Pharmacology of PEA

The rate- limiting constraint on PEA is its catabolism: a central half- life of only minutes renders the endogenous signal subtle and transient. Genetic evidence confirms that MAO- B is the principal regulator of PEA in vivo: MAO- B- deficient mice exhibit markedly elevated brain PEA [34]. Selective MAO- B inhibition removes this constraint, increasing and sustaining central PEA levels and thereby amplifying its combined actions — TAAR 1 signaling, substrate- type catecholamine release, and firing- coupled enhancement. Evidence from the deprenyl/selegiline literature establishes that this shifts PEA from a fleeting modulatory signal to a sustained one with behavioral and functional significance. Critically, this signal differs in nature from that of the comparator drugs: PEA augments impulse- coupled exocytotic release rather than driving firing- independent efflux or blocking clearance, thereby preserving the physiological temporal patterning of transmission, while TAAR 1 autoregulation provides negative feedback. This mechanism may therefore approach desirable catecholaminergic states — focus, drive, clean arousal, and elevated affect — without introducing the rapid- onset, high- occupancy reinforcement kinetics associated with the dependence liability of cocaine and amphetamine. The Sabelli program (Section 8.1. 1) provides a human proof of concept: PEA, rendered persistently active through selective MAO- B inhibition, produced a sustained effect without eliciting tolerance.

The MAO- B constraint is not static, and its trajectory is itself informative. Brain MAO- B activity rises substantially with age in healthy humans [35] and is further elevated in reactive astrocytes during neurodegeneration and following neurotrauma. This has two simultaneous effects. By accelerating PEA catabolism, rising MAO- B progressively attenuates the endogenous catecholaminergic signal in populations — older adults and individuals with brain injuries — in whom catecholaminergic drive is already declining. At the same time, MAO- B catalysis is a source of hydrogen peroxide and oxidative stress: selective elevation of astrocytic MAO- B alone is sufficient to produce nigral dopaminergic degeneration and a parkinsonian phenotype in vivo [36], while traumatic brain injury involving loss of consciousness is associated with a higher population- level incidence of subsequent Parkinson' s disease [37]. The catecholaminergic nuclei most affected in these states — the dopaminergic substantia nigra and the noradrenergic locus coeruleus — are the same systems supported by PEA' s impulse- coupled activity. Rising MAO- B is therefore consequential in two ways: it removes a physiological modulator while promoting oxidative loss of the neurons that the modulator supports. This convergence makes selective, titratable MAO- B protection mechanistically coherent in the context of aging and neurodegeneration, independently of any single clinical indication.

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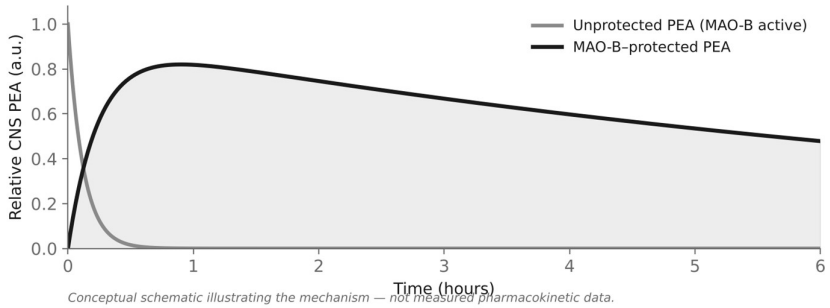

Figure 4. Selective MAO-B protection converts a minute-scale signal into a sustained one. Relieving the MAO-B catabolic constraint sustains central PEA, converting a transient endogenous signal into a functionally meaningful one (conceptual).

10.1. Determinants and Safety Parameters

Any strategy that relies on enzymatic protection of PEA is governed by a small number of parameters that are simultaneously the levers of efficacy and the determinants of safety. First and foremost is MAO-B selectivity: the potentiation must derive from selective MAO-B inhibition, because concurrent MAO-A inhibition, in the presence of PEA and dietary tyramine, carries hypertensive and serotonergic risk (the classic monoamine-oxidase-inhibitor interaction). Second is the drug-interaction surface: any MAO-inhibiting agent intersects with serotonergic and sympathomimetic medications, a consideration central to safety at a population level. Third is the degree and reversibility of inhibition, which sets the magnitude of PEA elevation and hence of effect, and which a reversible, selective inhibitor allows to be titrated while preserving the self-limiting character. Fourth is interindividual variability in MAO-B activity and baseline catecholaminergic tone, which shapes the window within which the effect is both perceptible and well tolerated.

11. The neuroendocrine and Aging Dimension

Beyond its acute and disorder-related effects, PEA occupies a defined place in two converging neuroendocrine accounts of aging, both centered on the catecholaminergic system.

11.1. Knoll: Catecholaminergic Decline and Enhancer Regulation

Within Knoll's enhancer-regulation framework, catecholaminergic activity peaks at sexual maturity and gradually declines thereafter [6]. The rate of decline is associated with learning capacity, drive, and lifespan: organisms that perform better and live longer possess a more active catecholaminergic system that deteriorates more slowly. Knoll proposed that this system can be enhanced at any stage of life by a mesencephalic enhancer substance—PEA being the endogenous prototype, with selegiline and (−)-BPAP as the studied derivatives—and reported that chronic administration of enhancers prolonged lifespan and preserved performance in rodents (Section 8.4).

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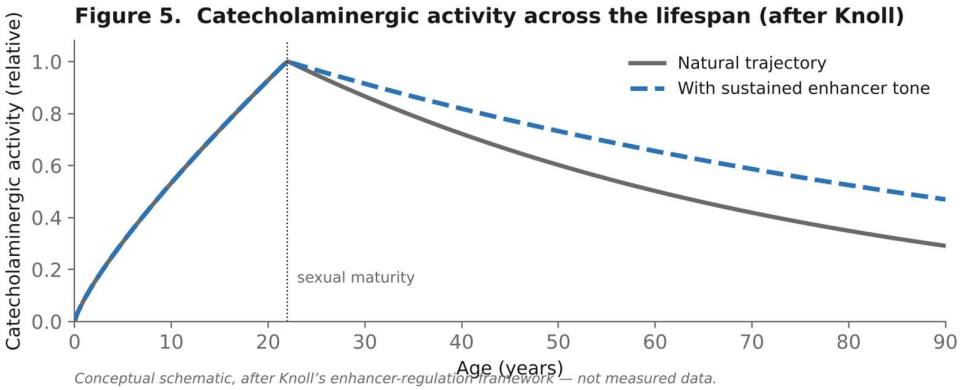

Figure 5. Catecholaminergic activity across the lifespan (after Knoll). In Knoll's framework, catecholaminergic activity peaks at maturity and declines thereafter; sustained enhancer tone is proposed to slow that decline (conceptual).

11.2. Dilman: The Neuroendocrine Theory and Its Corrective Strategies

Dilman's neuroendocrine theory [38] locates aging in the brain's regulatory centers, attributing post-maturational metabolic drift and age-related diseases to a progressive decline in hypothalamic sensitivity to feedback, with catecholaminergic signaling implicated in this process. Based on this framework, Dilman and Dean developed a set of corrective strategies [39] to address catecholaminergic insufficiency and neurotransmitter imbalance: increasing neurotransmitter production and activity, reducing MAO-B-mediated breakdown, correcting the catecholamine/serotonin ratio, inhibiting reuptake, and restoring receptor sensitivity.

11.3. PEA at the Intersection

PEA engages several of these mechanisms simultaneously: it increases catecholamine release and activity, serves as the preferred MAO-B substrate (so MAO-B protection both preserves PEA and reduces catecholamine catabolism), affects the catecholamine–serotonin balance, and promotes carrier-mediated release through TAAR1-coupled transporter modulation. Within both frameworks, sustaining endogenous enhancer tone throughout the post-developmental lifespan is a coherent objective, and PEA—when relieved of its MAO-B ceiling—is the endogenous agent positioned to achieve it.

For completeness, the two frameworks are not identical: Knoll emphasizes catecholaminergic decline that is to be reversed through enhancement, whereas Dilman's elevation formulation emphasizes a rising hypothalamic threshold. The accounts are reconciled in the clinical-gerontology lineage of Dilman and Dean through the shared endpoint of catecholaminergic insufficiency and loss of regulatory sensitivity. However, the mechanistic divergence is noted here and remains a subject for direct study.

12. Principal Findings

The comparative analysis developed in the preceding sections yields seven findings.

1. Distinct mechanism. PEA reaches the catecholaminergic state shared by psychostimulants through a mechanism that is categorically distinct from theirs. Cocaine sustains synaptic dopamine by blocking reuptake at the transporter; amphetamine induces non-exocytotic efflux by reversing the transporter and redistributing vesicular stores; and modafinil promotes wakefulness through weak, dopamine-transporter-dependent occupancy, coupled with downstream orexinergic and histaminergic drive. PEA combines TAAR1 agonism with impulse-propagation-coupled potentiation of endogenous catecholamine and serotonin release. It is cleared by MAO-B within minutes, thereby

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amplifying the neuron's own firing rather than imposing a sustained, firing-independent elevation (Section 2).

2. Endogenous parent of the class. PEA is the endogenous structural parent of the amphetamines: amphetamine is α-methyl-PEA, the same molecule bearing a single methyl substituent that blocks MAO-B catabolism and converts a transient endogenous signal into a long-acting, abusable drug. The pharmacological distance between the two is one methyl group and the enzymatic protection it confers (Sections 2 and 10).

3. Lower abuse liability. The mechanistic difference corresponds to a substantially lower abuse-liability profile. PEA can substitute for an amphetamine discriminative stimulus and is reinforcing under conditions that prevent its degradation. However, under physiological conditions, its clearance by MAO-B within minutes truncates the interoceptive and reinforcing signal before escalating, compulsive reward can develop. Its self-limiting pharmacokinetics, rather than an absence of intrinsic activity, account for the divergence in dependence liability (Sections 6 and 10).

4. Deficiency in catecholaminergic disorders. Reduced PEA levels or turnover are associated with disorders characterized by diminished catecholaminergic drive. Lower levels of PEA or its principal metabolite have been reported in major depression, attention-deficit phenotypes—with urinary PEA levels increasing during methylphenidate treatment [22,24]—and the cerebrospinal fluid of patients with Parkinson's disease [33]. These findings indicate associations rather than causation; however, they consistently link PEA deficiency with reduced drive, attention, and motivation (Sections 8 and 9).

5. Human proof of concept. The available controlled human evidence indicates that MAO-B-protected PEA produces a sustained antidepressant effect without tolerance: in Sabelli's program, oral PEA with low-dose selegiline produced a response in roughly 60% of depressed patients, durable on re-examination at 20–50 weeks in the large majority of responders and without dose escalation [20]. This evidence derives chiefly from open clinical studies in limited samples and has not been replicated in large randomized controlled trials; it constitutes a proof of concept for the enzymatic-protection strategy rather than definitive efficacy data (Section 8).

6. MAO-B as rate-limiting governor. MAO-B serves as the rate-limiting regulator of the PEA system, and its activity is dynamic. Genetic deletion of MAO-B markedly increases brain PEA [34]. Brain MAO-B activity increases with age in healthy humans [35] and is further elevated in neurodegeneration and following neurotrauma, where its catalytic activity contributes to oxidative dopaminergic loss [36,37]. Accordingly, increased MAO-B activity attenuates the endogenous PEA signal in populations in whom catecholaminergic drive is already declining (Section 10).

7. Unmet demand. Demand for catecholaminergic states is substantial and is currently met through harmful, illicit, or prescription agents, while PEA's own footprint remains negligible. Millions of people use cocaine, methamphetamine, and prescription and non-prescription stimulants, and millions more use prescribed stimulant medications. By contrast, PEA has no measurable population-level use as a functional agent, despite being endogenous and non-scheduled. The analysis therefore identifies a pharmacologically coherent, self-limiting endogenous modulator in the context of a documented and largely unmet demand (Section 7).

13. Discussion

These findings describe a molecule at an unusual point in pharmacology. β-Phenylethylamine is not an analog of the stimulants; it is their origin. The drugs that now bear nearly the entire burden of catecholaminergic enhancement—cocaine, the amphetamines, and, to a milder extent, modafinil—are structurally and mechanistically elaborations of a compound that the human brain already synthesizes and regulates. What distinguishes the endogenous parent from its pharmaceutical descendants is not the target, but the manner of engagement: PEA works in concert with neuronal firing and is extinguished within minutes, whereas synthetic agents override that firing and persist. The same chemistry that makes the descendants effective also makes them dangerous; the same chemistry that renders the parent self-limiting also makes it fleeting under current conditions.

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The comparatively limited development of PEA's functional pharmacology is better explained by incentives than by biology. Drug development operates under commercial motives, as does every pharmaceutical enterprise, and those motives favor patentable, scheduled molecules with defensible exclusivity over endogenous substances, which are difficult to protect and therefore difficult to fund. From this perspective, an endogenous catecholaminergic enhancer is precisely the kind of opportunity the prevailing model is structured to overlook: scientifically compelling yet commercially inconvenient. Its neglect reflects the economics of discovery, not the molecule itself. A sharper version of the same asymmetry is that an endogenous, self-limiting agent capable of occupying ground currently held by heavily abused and tightly scheduled drugs is attractive on public-health and safety grounds precisely because it resists commercialization: it cannot be made scarce. Reconsidering PEA as a functional psychostimulant in contexts where current pharmaceuticals are most abused is therefore an attractive proposition that runs directly counter to the patented-drug model.

The scientific case for revisiting PEA rests on its mechanism, rather than on a previously considered hypothesis. An endogenous modulator that amplifies rather than overrides, is governed by its own receptor- and enzyme-level autoregulation, and is self-limiting by design offers a fundamentally different risk architecture from releasers and reuptake inhibitors. It does so at precisely the point where those drugs fail the people who use them. The limiting factor has never been the biology; rather, it has been the minutes-scale catabolism that keeps the endogenous signal subtle. Selective enzymatic protection or delivery that withstands first-pass metabolism could render that signal functionally meaningful without recreating the reinforcement kinetics associated with dependence. The present moment is distinctive because of the convergence of an early but genuine human signal, a mechanism independently validated through TAAR1 and enhancer-regulation research [5,6,26], and substantial, documented, and growing demand that the current pharmacopeia addresses only at a cost.

A further consideration distinguishes PEA from the agents with which it is compared. Each of those drugs is defined by a narrow mechanism optimized for a single effect—reuptake blockade, forced release, or wake promotion—and is used for a correspondingly narrow indication. PEA acts more broadly: as an endogenous modulator, it influences dopaminergic, noradrenergic, and serotonergic transmission together; couples to the enhancer regulation that Knoll linked to drive, learning, and the age-related decline of catecholaminergic tone [6,32]; and operates within the body's own regulatory limits rather than against them. Its potential significance therefore need not be confined to a single indication. A regulator of catecholaminergic drive may be relevant to mood, motivation, attention, and the functional erosion associated with aging, as facets of a single underlying system. Such breadth is characteristic of endogenous modulators, and it is precisely what the single-target pharmaceutical template is poorly equipped to pursue.

The aging dimension warrants particular emphasis as a direction for study, rather than as a settled result. Catecholaminergic tone declines with age, MAO-B activity rises in parallel, and the hypothalamic and neuroendocrine systems dependent on catecholaminergic input lose sensitivity and precision—the deterioration that Dilman and Knoll, from different starting points, each placed near the center of functional aging [39]. If diminished PEA signaling contributes to this erosion, restoring it may constitute a rational target, not for an isolated symptom, but for the broader catecholaminergic and hypothalamic functions that decline over time and in the context of pathology. Whether endogenous enhancement can meaningfully restore those functions, and with what durability and safety, remains an open question that the present analysis can frame but not answer. This is among the more consequential avenues these findings open and warrants dedicated preclinical and controlled clinical study.

Taken as a whole, the analysis points less to a single therapeutic claim than to a category that modern neuropharmacology has largely left unexplored: endogenous, firing-coupled, self-limiting modulators of catecholaminergic drive. PEA is the natural prototype of this category—evidence that such an agent exists, is tolerated, and performs physiological work. Developing it on its own terms,

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rather than forcing it into the template of the drugs it resembles, is a rational next step and the one most likely to convert a century-old curiosity into a usable function. The question the field now faces is not whether the endogenous parent of the stimulants is pharmacologically interesting—the findings above establish that it is—but whether discovery incentives can be arranged to pursue what the biology has been offering all along.

13.1. Limitations

Much of the behavioral characterization of PEA is based on preclinical research. Controlled human data on sustained, protected administration remain limited, and the subjective effects and safety profile associated with selective, titrated MAO-B inhibition require formal investigation. In particular, the interaction profile of any MAO-inhibiting approach warrants systematic evaluation before exposure in a broader population. Accordingly, the arguments presented here provide a rationale for further investigation, not a substitute for it.

13.2. Priorities for Investigation

Several questions arise directly from the analysis and define a feasible research agenda:

1. A contemporary controlled trial. A randomized, placebo-controlled trial of MAO-B-protected PEA in an indication associated with deficiency would evaluate the Sabelli signal with contemporary rigor. No such trial has been conducted since that program, although the underlying mechanism has since been independently validated.

2. Pharmacokinetics of protected delivery. The plasma profile, effective half-life, and functional window achievable through selective MAO-B protection or first-pass-sparing delivery remain uncharacterized. These parameters will determine whether the endogenous signal can be made therapeutically meaningful.

3. Abuse liability under protected conditions. Self-administration, drug-discrimination, and conditioned-place-preference studies of PEA under conditions that slow its catabolism are needed to confirm that its self-limiting safety profile persists when the signal is prolonged.

4. Response stratified by deficiency. Determining whether baseline PEA or phenylacetic acid status predicts response would establish PEA restoration as a measurable, rational intervention and identify the populations most likely to benefit.

5. Mechanistic dissection. Quantifying the relative contributions of TAAR1 agonism and transporter-mediated release to PEA's functional effects would clarify the extent to which enhancement is possible while preserving a low-reinforcement profile.

14. Conclusion

β-Phenylethylamine is the endogenous precursor of a drug class whose members are sought by tens of millions of people, despite the risks of illegality, prescription controls, and pharmacologically determined harm. It acts on the same catecholaminergic substrate through a distinct, self-limiting mechanism, constrained by rapid MAO-B catabolism—a constraint that selective enzymatic protection can overcome. The combination of substantial unmet demand and a mechanistically differentiated, intrinsically safer endogenous agent presents a clear case for the controlled scientific development of PEA as a distinct category, separate from the stimulant drugs it closely resembles yet fundamentally differs from.

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References

1. Berry MD. Mammalian central nervous system trace amines: pharmacologic amphetamines, physiologic neuromodulators. J Neurochem. 2004;90(2):257–271. PMID:15228583.
2. Borowsky B, Adham N, Jones KA, et al. Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci USA. 2001;98(16):8966–8971. PMID:11459929; PMCID:PMC55357.
3. Lindemann L, Hoener MC. A renaissance in trace amines inspired by a novel GPCR family. Trends Pharmacol Sci. 2005;26(5):274–281. PMID:15718104.
4. Xie Z, Miller GM. Trace amine-associated receptor 1 as a monoaminergic modulator in brain. Biochem Pharmacol. 2009;78(9):1095–1104.
5. Xie Z, Miller GM. β-Phenylethylamine alters monoamine transporter function via trace amine-associated receptor 1. J Pharmacol Exp Ther. 2008;325(2):617–628. PMID:18182557.
6. Knoll J. Enhancer regulation / endogenous and synthetic enhancer compounds: a neurochemical concept of the innate and acquired drives. Neurochem Res. 2003;28:1187–1209.
7. Paterson IA, Juorio AV, Boulton AA. 2-Phenylethylamine: a modulator of catecholamine transmission in the mammalian central nervous system? J Neurochem. 1990;55(6):1827–1837.
8. Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science. 1987;237(4819):1219–1223. doi:10.1126/science.2820058. PMID:2820058.
9. Sulzer D, Sonders MS, Poulsen NW, Galli A. Mechanisms of neurotransmitter release by amphetamines: a review. Prog Neurobiol. 2005;75(6):406–433.
10. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. Annu Rev Pharmacol Toxicol. 2007;47:681–698.
11. Wisor JP, Nishino S, Sora I, et al. Dopaminergic role in stimulant-induced wakefulness. J Neurosci. 2001;21(5):1787–1794. PMID:11222668.
12. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology. 2008;33(7):1477–1502. doi:10.1038/sj.npp.1301534. PMID:17712350.
13. Nakamura M, Ishii A, Nakahara D. Characterization of β-phenylethylamine-induced monoamine release in rat nucleus accumbens: a microdialysis study. Eur J Pharmacol. 1998;349(2–3):163–169.
14. Sabelli HC, Javaid JI. Phenylethylamine modulation of affect: therapeutic and diagnostic implications. J Neuropsychiatry Clin Neurosci. 1995;7(1):6–14. doi:10.1176/jnp.7.1.6. PMID:7711493.
15. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2024 National Survey on Drug Use and Health. Rockville, MD: SAMHSA; 2025.
16. U.S. Drug Enforcement Administration / IQVIA. Report on Stimulant Trends. 2024.
17. United Nations Office on Drugs and Crime. World Drug Report 2024. Vienna: UNODC; 2024.
18. Sabelli HC, Mosnaim AD. Phenylethylamine hypothesis of affective behavior. Am J Psychiatry. 1974;131(6):695–699. doi:10.1176/ajp.131.6.695.
19. Sabelli HC, Fawcett J, Gusovsky F, et al. Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements. J Clin Psychiatry. 1986;47(2):66–70.

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20. Sabelli H, Fink P, Fawcett J, Tom C. Sustained antidepressant effect of phenylethylamine replacement. J Neuropsychiatry Clin Neurosci. 1996;8(2):168–171. doi:10.1176/jnp.8.2.168. PMID:9081552.
21. Szabo A, Billett E, Turner J. Phenylethylamine, a possible link to the antidepressant effects of exercise? Br J Sports Med. 2001;35(5):342–343. doi:10.1136/bjsm.35.5.342. PMID:11579070; PMCID:PMC1724404.
22. Baker GB, Bornstein RA, Rouget AC, et al. Phenylethylaminergic mechanisms in attention-deficit disorder. Biol Psychiatry. 1991;29(1):15–22. doi:10.1016/0006-3223(91)90207-3. PMID:2001444.
23. Kusaga A. Decreased β-phenylethylamine in the urine of children with ADHD and autistic disorder. No To Hattatsu. 2002;34(3):243–248.
24. Kusaga A, Yamashita Y, Koeda T, et al. Increased urine phenylethylamine after methylphenidate treatment in children with ADHD. Ann Neurol. 2002;52(3):371–374. doi:10.1002/ana.10302.
25. Scassellati C, Bonvicini C, Faraone SV, Gennarelli M. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. J Am Acad Child Adolesc Psychiatry. 2012;51(10):1003–1019. doi:10.1016/j.jaac.2012.08.015.
26. Revel FG, Moreau JL, Pozzi L, et al. A new perspective for schizophrenia: TAAR1 agonists reveal antipsychotic- and antidepressant-like activity. Mol Psychiatry. 2013;18(5):543–556. doi:10.1038/mp.2012.57. PMID:22641180.
27. Lee YJ, Kim HR, Lee CY, Hyun SA, Ko MY, Lee BS, Hwang DY, Ka M. 2-Phenylethylamine (PEA) ameliorates corticosterone-induced depression-like phenotype via the BDNF/TrkB/CREB signaling pathway. Int J Mol Sci. 2020;21(23):9103. doi:10.3390/ijms21239103. PMID:33265983; PMCID:PMC7729630.
28. Paulos MA, Tessel RE. Excretion of β-phenethylamine is elevated in humans after profound stress. Science. 1982;215(4536):1127–1129. doi:10.1126/science.6953460. PMID:6953460.
29. Bailey BA, Philips SR, Boulton AA. In vivo release of endogenous dopamine from rat caudate nucleus by β-phenylethylamine. Neurochem Res. 1987;12(2):173–178. [volume/pages to confirm]
30. Sandler M, Ruthven CRJ, Goodwin BL, et al. Deficient production of tyramine and octopamine in cases of depression. Nature. 1979;278(5702):357–358.
31. DeLisi LE, Murphy DL, Karoum F, et al. Phenylethylamine and phenylacetic acid excretion in affective illness. Am J Psychiatry. 1984;141(9):1055–1057. doi:10.1176/ajp.141.9.1055.
32. Knoll J. The Brain and Its Self: A Neurochemical Concept of the Innate and Acquired Drives. Berlin: Springer; 2005.
33. Shoji H, et al. Decreased β-phenylethylamine in cerebrospinal fluid in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;63(6):754. doi:10.1136/jnnp.63.6.754. PMCID:PMC1737214.
34. Grimsby J, Toth M, Chen K, et al. Increased stress response and β-phenylethylamine in MAOB-deficient mice. Nat Genet. 1997;17(2):206–210. doi:10.1038/ng1097-206.
35. Fowler JS, Volkow ND, Wang GJ, et al. Age-related increases in brain monoamine oxidase B in living healthy human subjects. Neurobiol Aging. 1997;18(4):431–435. doi:10.1016/S0197-4580(97)00037-7. PMID:9330975.
36. Mallajosyula JK, Kaur D, Chinta SJ, et al. MAO-B elevation in mouse brain astrocytes results in Parkinson's pathology. PLoS One. 2008;3(2):e1616. doi:10.1371/journal.pone.0001616. PMID:18286173; PMCID:PMC2229649.
37. Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: a Chronic Effects of Neurotrauma Consortium study. Neurology. 2018;90(20):e1771–e1779. doi:10.1212/WNL.0000000000005522.
38. Dilman VM. The Law of Deviation of Homeostasis and Diseases of Aging. Boston: John Wright PSG; 1981.
39. Dilman VM, Dean W. The Neuroendocrine Theory of Aging and Degenerative Disease. Pensacola: Center for Bio-Gerontology Press; 1992.

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