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Parkinson's disease, L-DOPA, and endogenous morphine: A revisit

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Summary

Clinical observations stemming from widespread employment of restorative L-3,4-dihydroxyphenylalanine (L-DOPA) therapy for management of dyskinesia in Parkinson's Disease (PD) patients implicate a regulatory role for endogenous morphine in central nervous system dopamine neurotransmission. Reciprocally, it appears that restorative L-DOPA administration has provided us with a compelling *in vivo* pharmacological model for targeting peripheral sites involved in endogenous morphine expression in human subjects. The biological activities underlying endogenous morphine expression and its interaction with its major precursor dopamine strongly suggest that endogenous morphine systems are reciprocally dysregulated in PD. These critical issues are examined from historical and current perspectives within our short review.

key words: **dopamine • L-DOPA • Parkinson's disease • morphine • tetrahydropapaveroline**

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Background

The discipline of endogenous morphine research has experienced a prolonged gestational period of nearly four decades, often marked by skepticism and prejudicial disregard from a significant portion of the scientific community. Within the last decade, however, a wealth of complementary biochemical, molecular, and physiological studies emanating from major independent laboratories has provided indispensable self-validating, foundation data sets to solidify the status of endogenous morphine research as a vital component of the biological sciences. Briefly, indisputable Q-TOF tandem mass spectrometry has confirmed the presence of low steady-state levels of chemically authentic morphine in diverse animal cells and organ systems [1–12]. Biochemical studies have characterized multiple enzyme-catalyzed reactions and chemically defined intermediate precursor molecules within a regulated biosynthetic pathway that display striking similarities to the plant biosynthetic scheme previously established in Papaver somniferum [1–35]. Preclinical and clinical studies have demonstrated regulated expression of endogenous morphine upon physiological demand in normative regulatory processes and in dysregulatory disease states [2–35]. As a unifying principle, our laboratory has identified and characterized a cellular "morphinergic" signaling pathway functionally linked to constitutive nitric oxide production and mediated by cognate mu3 and mu4 opiate receptors [13,18,22,36,37].

In light of the above, we engage the privilege of historical hindsight to propose that clinical observations stemming from widespread employment of restorative L-3,4-dihydroxyphenylalanine (L-DOPA) therapy for management of dyskinesia in Parkinson's Disease (PD) patients implicate a regulatory role for endogenous morphine in central nervous system (CNS) dopamine (DA) neurotransmission. Reciprocally, it appears that restorative L-DOPA administration has provided us with a compelling *in vivo* pharmacological model for targeting peripheral sites involved in endogenous morphine expression in human subjects.

Urinary Excretion of Morphine, Codeine, and Tetrahydropapaveroline by Parkinson's Disease Patients: Presumptive Evidence for L-DOPA as a Morphine Precursor

It is twenty years since the publication of a clinical report indicating an approximate 20 fold enrichment of morphine, codeine, and the benzylisoquinoline (BIQ) alkaloid tetrahydropapaveroline (THP, also called norlaudanosoline) in the urine of Parkinson's disease (PD) patients receiving L-DOPA replacement therapy, as compared to naive healthy controls [38]. The study was closely followed by a 1993 case report that quantified THP concentrations in the urine of 3 PD patients treated with L-DOPA-Carbidopa formulated as Sinemet [39]. In confirmation of the earlier report, the second study demonstrated marked increases in urinary THP concentrations that were roughly correlated with low, medium, and high administered dosages of L-DOPA-Carbidopa. These collected results provide putative evidence that endogenous morphine and codeine are synthesized *in vivo* utilizing L-DOPA and/or DA via the well characterized Pictet-Spengler condensation product THP [40–42] as an early intermediate precursor molecule. A later report demonstrated stereoselective expression of the (S) enantiomer of THP in human brain, thereby providing additional support for a regulated pathway of *de novo* synthesis of endogenous morphine via enzymatic O- and N-methyl transferase conversion of (S)-THP to (R)-reticuline [43].

Biological Signficance of Tetrahydropapaveroline as a Peripherally Expressed Morphine Precursor

Interestingly, the reports cited above are also confirmatory of a 1987 preclinical study demonstrating dramatic increases in rat brain concentrations of THP subsequent to peripheral co-administration of L-DOPA and ethanol [44]. Despite an excessively high concentration of ethanol (3 g/kg) that was administrated via the intraperitoneal route, it is apparent that a rapid synthesis of THP was accomplished over a 1–2 hour time frame. A first approximation of the rate of conversion of administered L-DOPA to THP yielded a value of approximately 0.1%. Of equal importance, a compartmental model emerges whereby THP is rapidly synthesized at peripheral sites, followed by rapid blood brain barrier transport into the CNS [45].

At this time, a cogent mechanism of peripheral THP biosynthesis in the presence or absence of ethanol has not been elucidated. Retrospectively, the contention of prominent scientists in alcohol addiction research that THP represents an aberrant and biologically deleterious DA derivative [40,42,46–52] that is markedly enhanced by ethanol, an ethanol metabolite such as acetaldehyde, or an enzyme involved in ethanol metabolism, i.e., acetaldehyde dehydrogenase appears to be critically flawed by the presence of THP in the urine of healthy, alcohol naïve, subjects [38]. Furthermore, the reluctance of alcoholism researchers to embrace THP as a naturally occuring morphine precursor is saliently at odds with preclinical studies demonstrating marked reductions of alcohol intake by opiate antagonists such as naloxone and naltrexone [53,54] and widespread clinical employment of naltrexone as a frontline pharmacotherapy for treatment of alcohol dependence [55].

In contrast to alcoholism research, there appeared to be a greater depth of critical thinking among PD researchers that pertained to positive and negative biological effects of THP and related tetrahydroisoquinoline alkaloids subsequent to L-DOPA administration. Despite a series of preclinical studies drawing a functional association between aberrant DA metabolism, cellular expression of THP and related tetrahydroisoquinoline alkaloids, and the etiology of PD [38,41,52,56–76], select clinical studies were supportive of positive therapeutic effects of pharmacologically administered morphine for treatment of PD dyskinesias [75,76]. Of potentially greater significance, a small body of biochemical and pharmacological studies demonstrated normative expression of THP and related tetrahydroisoquinoline alkaloids within the adrenal medulla and their associated regulatory activities on catecholamine synthetic and metabolic enzymes [57,68].

Spector's laboratory was the first to quantify relatively high concentrations of chemically authentic morphine and codeine in rat adrenal gland [77]. Interestingly, levels of the penultimate morphine precursor codeine were found to be greater than those of morphine, suggesting a precursor

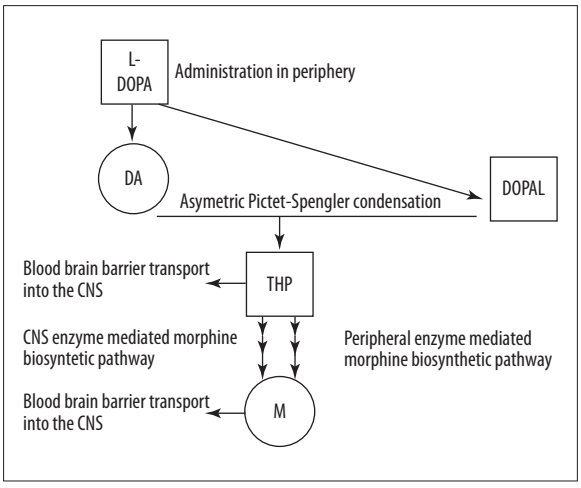

Figure 1. Biosynthesis of the putative morphine (M) intermediate precursor tetrahydropapaveroline (THP) proceeds via an asymmetric Pictet-Spengler condensation of dopamine (DA) and 3,4 dihydroxyphenylacetaldehyde (DOPAL) following peripheral administration of L- 3,4-dihydroxyphenylalanine (L-DOPA). Endogenous morphine is synthesized within peripheral sites via conversion of THP in an enzyme mediated biosynthetic pathway with striking similarities to that elucidated in *Papaver somniferum.* Conversely, THP may be directly transported into CNS and converted to endogenous morphine within a similar biosynthetic pathway.

to product biosynthetic relationship of the two opiate alkaloids in this glandular tissue. Relatively recently, our group has provided extensive empirical evidence supporting the role of the adrenal medulla as a major pheripheral site of endogenous morphine expression and physiological "hot spot" for opiate regulation of adrenergic sympethetic activities [2,4–7,9].

Based on the collective complementary lines of evidence presented above, we propose that restorative L-DOPA therapy for chronic management of PD patients represents an *in vivo* substrate loading model of rapid THP synthesis within peripheral sites, notably the adrenal medulla. Consistent with previous biochemical analyses [78,79], THP is further converted to key intermediate precursors within the morphine biosynthetic scheme, i.e., reticuline and salutaridine, at additional peripheral sites such as the liver, or is rapidly transported into the CNS. In support of these contentions, a prior clinical report has monitored relatively high concentrations of morphine and codeine in the cerebrospinal fluid (CSF) of healthy, opiate naïve, human volunteers [80] and implicates a regulatory role for endogenous morphine in normative CNS DA neurotransmission and as a potent restorative agent expressed from pharmacological administration of L-DOPA to PD patients.

Conclusions

Historically, the identification of THP as a biologically active Pictet-Spengler condensation product of DA and 3,4-dihydroxyphenylacetaldehyde (DOPAL) preceded the identification of low steady-state levels of immunologically detectable morphine in several species of mammalian brain [81,82]. A similar enzymatic step in Papaver somniferum is mediated by the biosynthetic enzyme nococlaurine synthase that catalyzes an asymmetric Pictet-Spengler condensation of DA and 4-hydroxyphenylacetaldehyde to yield (S)-norcoclaurine, the plant equivalent of THP [83] (Figure 1).

De novo biosynthesis and utilization of endogenous morphine by animal systems is governed by a complex set of regulatory controls that reflect both evolutionary conservation and divergent adaptation of biochemical, molecular, and cellular processes required for the emergence, elaboration, and maintenance of DA-ergic and related catecholaminergic signaling systems [76,84].

Morphine, DA, and catecholamine synthesis and metabolism share a similar set of L-Tyrosine-related substrates and enzymes activities. The role of endogenous morphine as an evolutionary model in the adaptation and maintenance of DA and catecholamines as predominant signaling molecules in relatively simple and complex nervous/CNS structures defines its biological presence as an autocrine/paracrine regulator of cellular homeostasis [36,37,84–86]. The biological activities underlying endogenous morphine expression and its interaction with its major precursor DA strongly suggest that endogenous morphine systems are reciprocally dysregulated in PD [87,88].

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