Review Article

Psychiatric Implications of Endogenous Morphine: Up-To-Date Review

(morphine / opiate receptors / psychiatry / dopamine / mania / depression / schizophrenia / autism / CYP2D6)

R. M. KREAM[1], G. B. STEFANO[1], R. PTÁČEK[2]

[1]Neuroscience Research Institute, State University of New York at Old Westbury, New York, USA
[2]Charles University in Prague, First Faculty of Medicine, Department of Psychiatry, Prague, Czech Republic

Abstract. For over 30 years empirical studies have repeatedly demonstrated that the biosynthesis of morphine by diverse animal and human tissues occurs. Recently, the blue mussel's neural tissues and human white blood cells were used to demonstrate the *de novo* biosynthesis of morphine for small precursor molecules derived from the aromatic amino acid L-tyrosine. Because catecholamine precursors, i.e., L-3,4-dihydroxyphenylalanine (L-DOPA), were also found to be utilized as morphine precursors, a novel reciprocally interactive mechanism is apparent that links catecholamine and opioid pathways in the activation and inhibition of diverse tissue responses. Additionally, these observations provide new insights into morphinergic signalling that transcend analgesia and addiction. We have also linked the biological effects of nitric oxide into a common effect in endogenous morphine signalling. Given the singular importance of dopamine and morphine's interaction in the CNS, the presence and association of this signalling with nitric oxide all promises to provide novel answers for mental health phenomena, which have been lacking because of the inability in accepting the empirical endogenous morphine studies.

Introduction

Morphine, a major and active constituent of opium, has long been used by humans for its relief of pain. In attempting to discover how morphine, an active ingredient in opium, works, it was first found that animal tissues contain specific molecules, which originally turned out to be opioid peptides, i.e., enkephalins, along with corresponding opioid receptors, which mimicked and were responsible for morphine's analgesic properties (Pasternak, 1988; Reisine and Bell, 1993; Reisine, 1995). In the last 25 years evidence also demonstrated that opiate alkaloids, i.e., morphine, were also endogenous chemical messengers along with their own stereoselect receptors (Gintzler et al., 1976; Gintzler et al., 1978; Stefano et al., 1993). The biosynthesis of morphine and the cloning of novel µ3/4 opiate receptors, shown to be opioid peptide insensitive and opiate alkaloid selective, in human demonstrated the endogenous status of this new chemical messenger. Cells, including neural tissues along with human stem cells and corresponding invertebrate tissues, demonstrate the ability of animal tissues to make morphine (Stefano et al., 1993; Cadet et al., 2003a, 2007; Boettcher et al., 2005a; Zhu et al., 2005a, b).

Endogenous Morphine

Biochemical, pharmacological, and physiological investigation into the expression and utilization of endogenous morphine by animal systems has presented an ongoing challenge to several research groups for over thirty years. Recent breakthrough data from our laboratory indicate:

1) The presence of low steady-state levels of chemically authentic morphine, as validated by Q-TOF tandem mass spectrometry, in invertebrate nervous tissues, primary cultures of human white blood cells – WBC (i. e. macrophages, neutrophils, and in the CNS, microglia and astrocytes), and in the rat adrenal medullary PC12 cell line.

2) The ability of a related set of small molecules including L-aromatic amino acid L-tyrosine (L-TYR), its monoamine homologue tyramine (TA), L-3,4-dihydroxyphenylalanine (L-DOPA), and dopamine (DA) to significantly increase cellular morphine concentrations in these same tissue preparations, presumably via *de novo* biosynthetic mechanisms (Stefano et al.,

Abbreviations: BIQ – benzylisoquinoline, CSF – cerebrospinal fluid, DA – dopamine, HVA – homovanillic acid, L-DOPA – L-3,4-dihydroxyphenylalanine, L-TYR – L-tyrosine, MLC – morphine-like compound, NO – nitric oxide, TA – tyramine, TH – tyrosine hydroxylase, THP – tetrahydropapaveroline, VTA – ventral tegmental areas, WBC – white blood cells.

1993, 2002, 2003, 2004a, b; Brix-Christensen et al., 2000; Goumon and Stefano, 2000; Goumon et al., 2000a-c, 2001, 2005; Guarna et al., 2002; Cadet et al., 2003a, 2004; Zhu and Stefano, 2004; Casares et al., 2005; Dusek et al., 2006; Zhu et al., 2001a-c, 2002a, b, 2003, 2004a, b, 2005a-c, 2006a-d).

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 signalling systems (Stefano and Kream, 2007). In simple terms, morphine, DA, and catecholamine synthesis and metabolism share a similar set of L-TYR-related substrates and enzyme activities (Kream and Stefano, 2006; Kream et al., 2007). The role of endogenous morphine as an evolutionary chaperone in the adaptation and maintenance of DA and catecholamines as predominant signalling molecules in relatively simple and complex nervous/CNS structures defines its biological presence as an autocrine/paracrine regulator of cellular homeostasis.

Historical Basis for Reciprocal Regulation of DA and Endogenous Morphine within the CNS

Curiously, initial speculations as to the existence and potential physiological role of endogenous morphine were made over 30 years ago by prominent researchers in the field of alcohol abuse, not opioid abuse, who advanced the hypothesis that the reinforcing or addictive effects of ethanol were functionally linked to the cellular effects of naturally-occurring DA-derived isoquinoline alkaloids, notably the benzylisoquinoline (BIQ) tetrahydropapaveroline (THP, also called norlaudanosoline), a recognized intermediate precursor of morphine in the plant biosynthetic pathway (Halushka et al., 1970; Walsh et al., 1970; Weiner, 1978; Clow et al., 1983; Myers, 1990; Duncan and Fernando, 1991; Myers and Robinson, 1999; Sallstrom et al., 1999). Additionally, the functional association between aberrant DA metabolism, cellular expression of isoquinoline alkaloids, and the aetiology of Parkinson's disease was intensively investigated during this period (Heikkila et al., 1971; Johnston, 1971; Greenberg and Cohen, 1973; Sandler et al., 1973; Davis et al., 1975; Katz and Cohen, 1976; Coscia et al., 1977; Britton, 1982; Galloway et al., 1982; Sandler et al., 1982; Nimit et al., 1983; Suzuki et al., 1990; Matsubara et al., 1992; Niwa et al., 1992; Naoi et al., 1998; Okada et al., 1998; Berg et al., 1999, 2001; Cadet et al., 2003a,b; Soh et al., 2003; Collins, 2004; Shin et al., 2004; Kim et al., 2005; Fricchione and Stefano, 2005), resulting in considerable cross-fertilization of scientific expertise between alcohol abuse and Parkinson's disease researchers.

By the early 1970's, a functional association between L-DOPA therapy and *in vivo* formation of THP had been proposed and it was subsequently demonstrated that urinary levels of morphine, codeine, and THP in L-DOPA-treated Parkinsonian patients are dramatically elevated as compared to matched controls and abstinent alcoholics (Cadet et al., 2003b; Kream and Stefano, 2006). Inferential support for THP and other BIQs as biosynthetic intermediates in endogenous morphine production was provided by the extensive data sets evolving from alcohol and Parkinson's disease research. Here inconclusive, often contradictory, evidence indicated that non-physiological concentrations of isoquinoline alkaloids, often in the millimolar range, were required to mediate cellular toxicity via down-regulation of necessary DA metabolism and turnover linked to free radical production. Because biologically meaningful concentrations of BIQ alkaloids were often observed to have little or no effect on DA metabolism and cellular integrity, a null hypothesis was apparent indicating different, potentially important, regulatory activities for this class of biomolecules outside the realm of DA signalling, i.e., endogenous morphine biosynthesis.

A morphine-like compound (MLC) in animal tissues was originally demonstrated by immunological recognition (Gintzler et al., 1976). Histologically, morphine-like immunoreactivity has been demonstrated in cell bodies, fibres and terminals of neurons in different brain areas of the rat (Bianchi et al., 1993a), mouse (Gintzler et al., 1978) and man (Bianchi et al., 1994a), revealing numerous nerve cell bodies with variable morphology, dendrites and nerve fibres throughout the cerebral cortex, caudate putamen, granule cells of dentate gyrus and dorsal hippocampus, and brainstem. In human brain tissue, morphine-like immunoreactivity was identified in cerebral and cerebellar cortex. Subsequently, endogenous MLCs have been identified in mouse, rat and calf brain (Gintzler et al., 1978; Killian et al., 1981; Zhu et al., 2004a). Purified MLC has been chromatographically and chemically characterized by tandem mass spectrometry to represent a chemically authentic substance in various tissues such as bovine brain, rat and mouse brain, hypothalamus and adrenal glands, mammalian lung, invertebrate and human tissues, human cerebrospinal fluid and human plasma (Gintzler et al., 1976; Goldstein et al., 1985; Donnerer et al., 1986; Cardinale et al., 1987; Donnerer et al., 1987; Stefano et al., 1993; Munjal et al., 1996; Bilfinger et al., 1997; Guarna et al., 1998; Goumon and Stefano, 2000; Goumon et al., 2000a,c). Codeine and morphine also have been identified in human cerebrospinal fluid (Cardinale et al., 1987) and non-human primate brain (Neri et al., 2004). Morphine precursors, reticuline (Zhu et al., 2003), thebaine (Kodaira et al., 1989) and codeine (Epple et al., 1993; Munjal et al., 1996; Hofmann et al., 1999) are some of the main intermediates of morphine biosynthesis in the poppy plant and have been found in mammals.

The pathway for morphine biosynthesis has recently been demonstrated in neuroblastoma cells lines and in-

vertebrate nervous tissues and in human white blood cells (Boettcher et al., 2005b; Zhu et al., 2005a,b), building on previous works utilizing precursors (Donnerer et al., 1986; Weitz et al., 1987; Kodaira and Spector, 1988; Goumon et al., 2000b; Zhu and Stefano, 2004) (Fig. 1). Key observations from these studies indicate that L-TYR, its monoamine homologue TA, and their respective catechol derivatives, L-DOPA and DA serve as substrates for *de novo* morphine production and that pharmacological characterization of TA utilization as a morphine precursor indicates one or more catalytic steps mediated by microsomal cytochrome P-450 2D6 (CYP2D6) (Zhu et al., 2005a,b) (Fig. 1). The significance of TA as a biosynthetic intermediate is validated by *in vitro* enzyme kinetic studies demonstrating DA formation via CYP2D6-catalysed ring hydroxylation of TA (Hiroi et al., 1998; Miller et al., 2001; Guengerich et al., 2002; Niwa et al., 2004), which in turn lends support to the existence of a potentially important TH-independent pool of cytosolic DA that is available for endogenous morphine expression (Zhu et al., 2005a-c).

These data also effectively present a case for separate and distinct cellular pools of L-TYR-derived substrates targeted for *de novo* morphine synthesis in animal cells, and reject previously published biosynthetic schemes, indicating that THP production is exclusively derived from DA (Davis and Walsh, 1970; Davis et al., 1970; Halushka et al., 1970; Walsh et al., 1970; Yamanaka et al., 1970; Weiner, 1978; Collins, 2004). Our formulated model establishes a *stoichiometric* relationship of one molecule of DA, derived from L-DOPA decarboxylase (DDC)-catalysed decarboxylation of L-DOPA or CYP2D6-catalysed ring hydroxylation of TA, to one molecule of 3,4-dihydroxyphenylacetaldehyde derived directly from L-DOPA without intermediate conversion to DA, thereby rejecting the long held hypothesis that monoamine oxidase (MAO) is a key enzyme involved in THP formation *in vivo* (Halushka et al., 1970; Walsh et al., 1970; Johnston, 1971; Sandler et al., 1973; Turner et al., 1974; Davis et al., 1975; Weiner, 1978; Collins et al., 1979; Kream et al., 1980; Weiner, 1981; Britton, 1982; Sandler et al., 1982; Arai et al., 1998; Collins, 2004). Thus, we have demonstrated that DA is a precursor for morphine biosynthesis in animal tissues coupling it to DA involvement in mental health, i.e., schizophrenia, depression.

Recently, the μ_3-opioid receptor (M3R) was cloned by our laboratory in human neural, immune and vascular tissues (Cadet et al., 2003a). The M3R, a splice variant of the full-length μ-opioid receptor (MOR) transcript, is activated by morphine and related morphinan opiate alkaloids and does not recognize endogenous opioid peptides of their chemically modified analogues. Importantly, the M3R is coupled to cellular nitric oxide synthase (cNOS), resulting in nitric oxide (NO) production and release (Stefano et al., 2000b). In rat limbic tissues (hippocampus and amygdala) morphine is present as demonstrated by biochemical, including mass spectrometry, and immunocytochemical techniques (Bianchi et al., 1993a, 1994a; Spector et al., 2001; Zhu et al., 2004a). Additionally, adding exogenous morphine to these tissues results in NO release, which does not occur with opioid peptides, indirectly demonstrating the M3R (Cadet et al., 2003a). In addition, the G protein-coupled receptor is 6 not 7 transmembrane, indicating its primordial nature since it is also present in invertebrates and human stem cells (Cadet et al., 2007; Kream et al., 2007). Taken together, a highly specific postsynaptic receptor exists in these tissues for morphine, demonstrating its action as a neurotransmitter.

The involvement of nitric oxide as an end-product regulator of endogenous morphinergic and DA-ergic signalling is compelling. It inhibits tyrosine hydrolase (TH), catechol-O-methyltransferase (COMT) and CYP2D6, key enzymes in both DA and morphine biosynthesis (Gonzalez et al., 1998; Abreu et al., 2000; Stefano et al., 2001; Hara and Adachi, 2002; Mantione et al., 2008). Nitric oxide has also been proposed as one of the main manifestations of morphine signalling (Stefano et al., 1995; Liu et al., 1996; Stefano and Scharrer, 1996, Stefano et al., 1996b, 2000a, b; Goumon et al., 2000b; Cadet et al., 2003a; Pryor et al., 2005), placing it in a pivotal role in determining how endogenous morphine works in mental health neural processes. This hypothesis is made even more compelling given the proposed links of the endogenous morphine system to mental health since it can function as a neurotransmitter within the central nervous system, a hypothesis supported by its anatomical localization as well as functional relevance, i.e., memory (Bianchi et al., 1993b, 1994b, Fricchione et al., 1994; Stefano et al., 1996b, 2000b, 2002, 2005; Guarna et al., 1998, 2004, 2005, Neri et al., 2004; Fricchione and Stefano, 2005)**.**

We have already demonstrated that cocaine, alcohol and nicotine have the ability to enhance endogenous morphine processes at a common step, e.g., release from cellular stores, in invertebrate and human tissues (Zhu et al., 2006b-e), which may affect brain reward centres, i.e., motivation. By understanding endogenous morphine signalling we may finally understand the ravages of neural processes associated with mental health and how we may treat them more effectively.

Mental Health

Finally, additional data from our group indicates an approximate 3-fold enhancement of tissue concentrations of endogenous morphine following administration of THP to an *ex vivo* preparation of invertebrate ganglia (Zhu et al., 2005b). The observed rate of conversion of THP to morphine of approximately 20 % when compared to the low steady-state levels of tissue THP suggested high intrinsic clearance of THP and other morphine precursors through a defined cellular biosynthetic pathway.

Recognition and elucidation of evolutionarily conserved and adapted mechanisms that govern the chemical integrity and utilization of catechol- and BIQ-de-

rived signalling molecules will dramatically facilitate the establishment of a unified biochemical and molecular foundation for key future studies into the underlying mechanisms of mental health. Furthermore, NO modulates this pathway since it has been shown to mediate enzymes in the morphine biosynthetic pathway, i.e., TH and CYP2D6 (Gonzalez et al., 1998; Abreu et al., 2000; Stefano et al., 2001; Hara and Adachi, 2002; Mantione et al., 2008). The relevance of this regulation is made even more significant by the fact that morphine and morphine-6-glucuronide stimulate constitutive NO release in many animal and human tissues via its coupling to the M3R (Stefano et al., 1995, 1996b, 2000a,b; Liu et al., 1996; Stefano and Scharrer, 1996; Goumon et al., 2000b; Cadet et al., 2003a; Pryor et al., 2005). Thus, the coupling to NO release may represent a negative feedback mechanism involved in the modulation of endogenous morphine expression.

Most of the scientific enthusiasm for studying the potential importance of opioid and opiate signalling in psychiatric disorders such as schizophrenia and affective illnesses was evident in the late 1970's and 1980's soon after the discovery of endogenous opioid neuropeptides (Fig. 2). In 1977 a review of morphine's potential role as an antipsychotic agent was published (Comfort, 1977) and a case series study in 1978 revealed that endorphin levels in the cerebrospinal fluid were elevated in acutely ill schizophrenic, bipolar and postpartum psychotic patients, returning to levels within the normal range after the psychotic stages ended (Lindstrom et al., 1978). Affective illness reports suggested that opiate agonists sometimes had mild antidepressant effects while naloxone occasionally benefited patients with mania (Cohen and Pickar, 1981; Extein et al., 1981). Short-term naloxone treatment was found to add benefit to patients with schizophrenia who remained on their neuroleptics (Pickar et al., 1982). Some researchers suggested based on both non-human primate and human studies that spontaneous panic states may relate to locus coeruleus (LC) norepinephrine hyperactivity based on an opioid neuropeptide deficiency syndrome leading to a failure of LC burst suppression (Gold et al., 1982). Such a condition might also predispose to other psychiatric syndromes, and endogenous opioid deficiencies have been implicated in stress-related states. When morphine 5 mg is administered, cortisol secretion is suppressed, however, in patients with major depression and abnormal dexamethasone suppression tests; there is early escape from suppression after initial suppression induced by morphine (Zis et al., 1983). There is also a diminished increase in serum prolactin after morphine 5 mg in depressed patients (Robertson et al., 1984). The maximum prolactin response of eight of 15 depressed patients was less than the lowest response of any of the normal subjects. This finding suggests that an abnormality exists in opioid and DA systems in depression since DA is a prolactin inhibitory factor. Basal cortisol but not basal prolactin levels were elevated in patients with anorexia nervosa and in depressed patients in another study (Zis et al., 1989). After morphine administration cortisol levels went down progressively in these groups as well as in normal controls. However, the prolactin response to morphine was attenuated significantly in the depressed cohort, consistent with the results of the other study described above.

In 1985 researchers suggested that the mild antipsychotic efficacy of opioids in patients suffering from schizophrenia may result from an interaction of opioids with the DA-ergic system (Schmauss and Emrich, 1985). Opioid modulation of DA-ergic functions had already been shown in anatomical and biochemical studies revealing an effect of opioid receptors on DA-ergic nerve terminals, cell bodies, and afferent nerve endings culminating in DA activities. Endogenous enkephalin levels correlate well with the endogenous DA concentrations in various brain areas. Morphine systemic or iontophoretic administration alters the spontaneous activity of ventral tegmental DA-ergic neurons. Morphine and enkephalin stimulate pituitary prolactin release, whereas DA inhibits it. Opioid agonists effectively alter DA release, DA reuptake, and DA metabolism in the striatum and substantia nigra. Conversely, chronic neuroleptic treatment enhances the synthesis and release of pituitary β-endorphin and prolactin through DA blockade. Phencyclidine, a psychotropic drug that shares certain pharmacological characteristics with the putative σ-opioid receptor ligand SKF 10,047, can indirectly lead to DA agonism resulting in prolactin release and the release of acetylcholine. This led to suggestions that an imbalance of the opiate-DA interaction might be involved in the pathogenesis of schizophrenia. With this in mind, clinical studies on the effects of opioids on psychotic symptoms should attempt to uncover how important opioid modulation of DA-ergic activity is in these patients.

In 1994, we speculated on the psychiatric implications of endogenous morphine (Fricchione et al., 1994; Stefano and Scharrer; 1994, Stefano et al., 1994), after reviewing evidence for the importance of the mesolimbic-mesocortical DA brain reward-motivation circuitries in the major psychiatric illnesses and of the endogenous opioids and opiates active at local μ receptors that modulate the mesolimbic-mesocortical DA activity (Fricchione et al., 1994). In 1996 we speculated further on these implications for specific diseases such as schizophrenia, depression and autism (Stefano et al., 1996a). The mesolimbic-mesocortical DA systems in addition to the mesostriatal DA system play important roles in schizophrenia, and μ receptor functioning may thus impact this disease state (Lipska and Weinberger, 1993). There are some schizophrenics who are now known to display hypofrontality with ventricular enlargement and atrophy on neuroimaging and frontal network syndrome on neuropsychological testing (Weinberger et al., 1992). It is known that damage sustained in the prefrontal cortex can reduce the threshold for activation of the mesolimbic DA system under stress conditions. This can lead to a state of hyperresponsiveness to stress. With prolonged social defeat stress there are changes in μ re-

ceptor mRNA expression and function in the ventral tegmental areas (VTA) of rats leading to changes in DA activity levels (Nikulina et al., 2005) (Fig. 2). Morphine immunoreactivity has been found in the hippocampus where disarray is found in schizophrenia (Bianchi et al., 1993c; Lipska and Weinberger, 1993). These findings raise the possibility that endogenous morphine, as a downstream product of the DA synthetic pathway and as a neuromodulator of the DA reward and motivation circuitries, may be involved in the pathophysiology of schizophrenia and this can now be studied. The link and regulation of morphine synthesis via DA becomes highly significant (Esch and Stefano, 2005; Fricchione and Stefano, 2005; Stefano et al., 2005, 2006; Esch et al., 2006; Fricchione et al., 2008; Neri et al., 2008; Stefano and Kream, 2008).

There is also evidence of mesolimbic DA system involvement in depression (Kapur and Mann, 1992). Lower cerebrospinal fluid (CSF) homovanillic acid (HVA) levels in depressed patients, increased incidence of depression in Parkinson's disease and with DA-depleting agents, the antidepressant effects of DA-ergic agents, and the enhancement of DA transmission with electroconvulsive therapy all point to a role for DA dysfunction in depressive disorders. Drugs such as cocaine, morphine, as well as psychostimulants and nicotine that result in self-administration due to reinforcement properties are associated with increased VTA DA neuron firing, activation of mesolimbic pathways, and an increase in nucleus accumbens extracellular DA concentration (DiChiara et al., 1990). The implications of these relationships for our understanding of depression are still unclear, but we can again speculate that a naturally occurring opiate, morphine, may be playing a role and that a reactivation of research in this area is warranted (Ste-

fano and Kream, 2007; Stefano et al., 2007; Mantione et al., 2008; Neri et al., 2008; Zhu et al., 2008) (Fig. 2).

We can also make the case that endogenous morphine is involved in the pathogenesis of autism, especially given the fact that narcotic antagonists such as naltrexone have shown some efficacy in reducing autistic symptomatology (Herman et al., 1986; Elchaar et al., 2006). This may reflect a defect in endogenous opioid (opiate) activity at the μ receptor in autism that requires a rebalancing through the use of a μ receptor blocker. In other words, certain forms of autism may result from over-activity at the μ receptor that can be blocked with opiate antagonists. On the other hand, endogenous opioid binding to μ receptors in the brain reward circuitry may be involved in infant attachment behaviour (Moles et al., 2004). In μ receptor knockout mice, fewer ultrasonic isolation cries are emitted for the separated mother and these mice do not show preference for maternal cues. Thus a total loss of μ receptor functioning in brain reward and motivation circuitries may also be invoked as a possible cause in some autism subtypes. Endogenous morphine would seem to be an important candidate neuromodulator of interest in the research quest to find the causes of infantile and childhood autism.

Recently, we have focused on the fact that DA is a major morphine precursor, which is quite an important fact given the role of DA in psychiatric disorders (Stefano and Kream, 2007). It is of interest to note while

Fig. 2. Hypothetical dopamine-morphine pathway in a reward context. A. With normal motivators present the reward system, which contains both DA and morphine, functions at normal low levels with slight elevations that may be considered to be appropriate for a novel positive event. B. Given external high substances that have the ability to bypass the normal circuitry via concentration saturation, normal cues are insufficient and the exogenous substances emerge as the new abnormal stimulus to achieve pleasure/reward, etc. Indeed, even an insufficiency in the normal levels of these agents (DA and morphine) would trigger this abnormal accentuated pathway simply to reach a proper reward state, which becomes difficult since these are poorly modulated external substances. Thus, morphine insufficiency may not be able to calm mental states leading to mania/depression, etc.
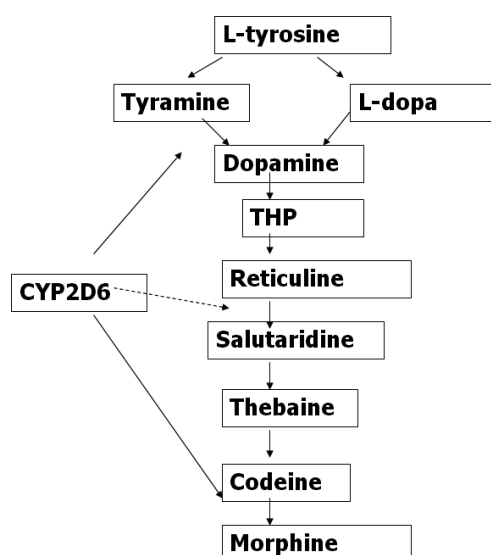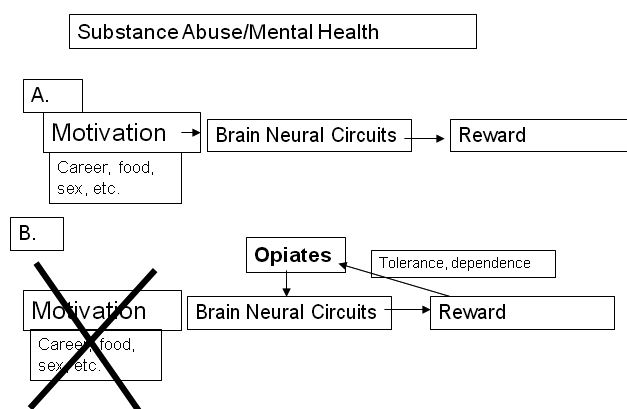
Fig 1. Biosynthesis of morphine in human white blood cells and invertebrate ganglia (Zhu et al., 2005a,b). Figure also demonstrates the significance of CYP2D6 in this process, which can be down-regulated via NO release from μ3 activation (Mantione et al., 2008).

plants make morphine and contain DA, as a precursor, DA plays no bioactive role (Stefano and Kream, 2007). In invertebrates both are also present, but DA plays a role in mobility and motivation. In this regard, very few animals appear to have norepinephrine. In vertebrates morphine's endogenous signal status is still present as is that of all the catecholamines. These data suggest it was the morphinergic system which gave rise to that of the catecholamines, which developed to enhance mobility and motivation-induced mobility (Stefano and Kream, 2007). Morphine's preeminent role was that of general down-regulation of tissue excitability, scavenging free radicals, lowering metabolism and instituting a state of calm. The catecholamines, on the other hand, are involved with motivation processes that lead to mobility, including states of high emotionality, which may also be used to override rationality if appropriate to induce activity (Stefano and Fricchione, 1995a,b).

Conclusion

In conclusion, with the recent discoveries documenting novel stereoselect 6 transmembrane opiate receptors and their coupling to constitutive nitric oxide release along with specific cells that make morphine, it appears that a new field of investigation has opened up. Needless to say it will extend into many of the current disciplines, especially those that have high vested interest in roles for catecholamines, i.e., DA. Endogenous morphine promises to grow and in so doing aid in our underlying beliefs dealing especially with mental health and substance abuse.

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