Catechol-O-methyltransferase: potential relationship to idiopathic hypertension

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Abstract

Catecholamine signaling pathways in the peripheral and central nervous systems (PNS, CNS, respectively) utilize catechol-O-methyltransferase (COMT) as a major regulatory enzyme responsible for deactivation of dopamine (DA), norepinephrine (NE) and epinephrine (E). Accordingly, homeostasis of COMT gene expression is hypothesized to be functionally linked to regulation of autonomic control of normotensive vascular events. Recently, we demonstrated that morphine administration in vitro resulted in decreased cellular concentrations of COMT-encoding mRNA levels, as compared to control values. In contrast, cells treated with E up regulated their COMT gene expression. In sum, these observations indicate a potential reciprocal linkage between end product inhibition of COMT gene expression by E and morphine. Interestingly, the observed effects of administered E on COMT gene expression suggest an enhancement of its own catabolism or, reciprocally, a stimulation morphine biosynthesis.

Key words: endogenous morphine, catecholamines, epinephrine, catechol-O-methyltransferase.

A "morphinergic" signaling pathway in endothelial cells

We have recently demonstrated a functional regulatory pathway in vascular endothelial cells driven by endogenous, chemically authentic, morphine, its cognate opiate alkaloid-selective μ_3 and μ_4 receptors and constitutive nitric oxide (NO) production and release [1-5]. Because NO/cyclic guanosine monophosphate (cGMP) signaling events have been well established as potent regulators of vasodilatation, it appears likely that populations of endothelial cells are also entrained as physiological regulators of normal vascular tone. Accordingly, μ_3 and μ_4 opiate receptors may represent important potential therapeutic targets for restoring normotensive vascular tone in hypertensive syndromes [1-5].

The presence of chemically authentic morphine has been demonstrated in vascular endothelial cells obtained from human atria [5] and human white blood cells (WBC), which also express μ_3 and μ_4 opiate receptors [1, 6], and several human cancer cell lines [1, 2, 5, 7, 8]. We have therefore hypothesized that μ_3 and μ_4 opiate receptors coupled to constitutive NO expression are tonically activated by low levels of endogenously expressed, chemically authentic morphine [5], a contention that is consistent with the presence of low levels of circulating morphine in human plasma

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[9-11]. Provocatively, we have also characterized a functionally competent μ_3/μ_4 receptor/NO-coupled regulatory pathway in human multilineage progenitor cells (MLPC) [12], thereby suggesting a fundamental role of morphine/NO-coupled developmental processes.

One of the key physiological roles of the "morphinergic"/NO-coupled regulatory pathway appears to be the homeostatic maintenance of normal vascular tone, which can only be achieved by intimate association of the vascular endothelium with circulating leukocytes. Endogenous morphine derived from defined cellular sources and circulating in plasma appears to provide an important caretaker role in promoting coordinated, on demand, vasomotor responsiveness, to diverse physiological stimuli.

Shared "morphinergic"/catecholamine biosynthetic enzymes

Based on recent elucidations of key functional components of "morphinergic" signaling pathways, it is likely that variations in gene expression of key enzymes of the morphine biosynthetic pathway may have profound effects on human health,

especially in immune and vascular tissues [13]. Furthermore, the establishment of dopamine (DA) as a requisite intermediate precursor molecule in the morphine biosynthetic pathway suggest that perturbations of these biosynthetic enzymes will significantly effect human behavioral responses to cognitive and physiological stressors [13-18].

Previously published studies have established catechol-O-methyltransferase (COMT) as a key player in the morphine biosynthetic pathway responsible for enzymatic conversion of tetra-hydropapveroline (THP) to the methylated intermediate precursor molecule (S)-reticuline [13, 16, 19]. Additionally, polymorphisms in other genes involved in "morphinergic" and catecholamine metabolic pathways, including tyrosine hydroxylase, DOPA decarboxylase, dopamine β-hydroxylase, and monoamine oxidase have not been as well studied as COMT in terms of their effects on human health [14-18, 20-25]. The most studied COMT polymorphism is termed val/met 158. This polymorphism has a methionine substituted for a valine at amino acid 158 [26]. Ongoing studies are attempting to establish a link between this polymorphism and behavior [27]. The effect of this
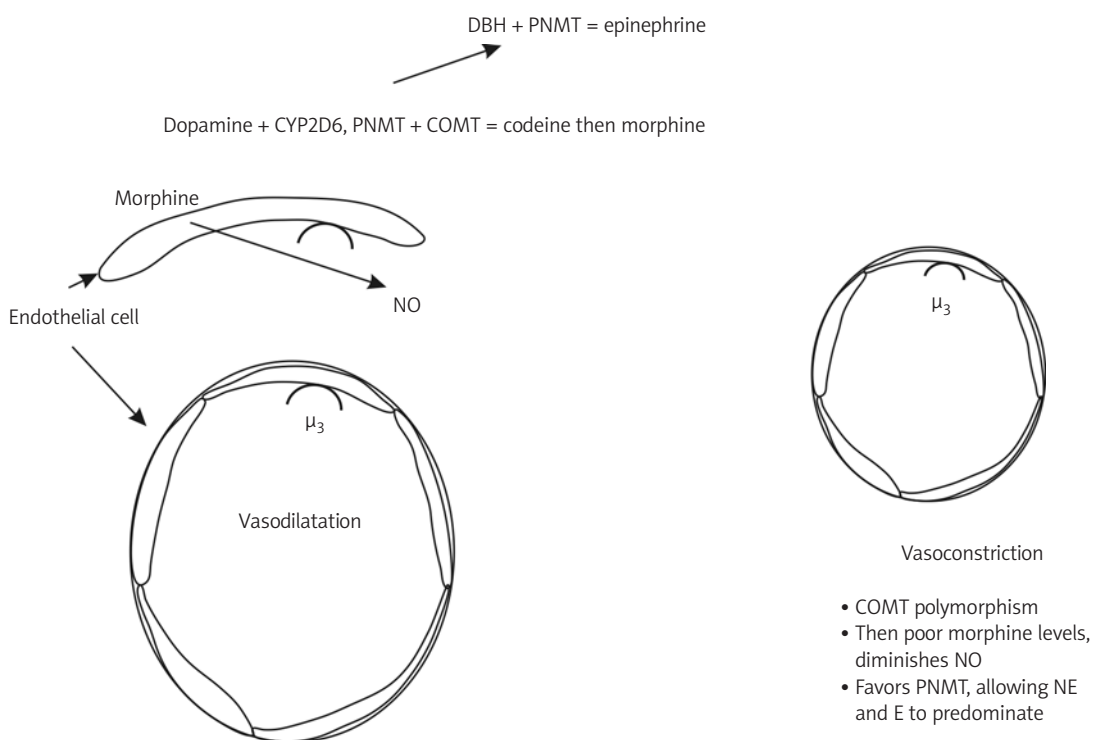
Figure 1. Human vascular endothelial cells contain the μ_3/μ_4 opiate receptor subtype coupled to NO release, leading to vasodilatation. Furthermore, vascular endothelial cells appear to express endogenous morphine, indicating an autonomous autocrine/paracrine signaling pathway. Well established polymorphisms of the COMT gene are predicted to result in significant alterations in morphine biosynthesis (discussed above). Alterations of COMT enzyme activity will effectively result in diminished cellular concentrations of endogenous morphine with coordinate reductions of NO signaling events, a compounded endpoint promoting enhanced vasoconstriction. Second, alterations of COMT enzyme activity will effectively diminish catecholamine metabolism, with resultant enhancement of NE and E pressor activity via α-adrenergic receptor activation

polymorphism is a lowering of the activity of COMT and thus a slower metabolism of DA [26, 28].

Recently we examined the effect of morphine exposure on COMT gene expression in cancer cells [29, 30]. Morphine administration was observed to decrease cellular concentrations of COMT-encoding mRNA in a time-dependent manner, thereby suggesting a negative feedback regulatory process. Interestingly, administration of E at 10^{-9}M to colonicadenocarcinoma cells at for 24 h was observed to produce a 1.6 fold increase in levels of COMT-encoding mRNA [30]. In sum, these observations indicated a potential reciprocal linkage between end product inhibition of COMT gene expression by E and morphine. Interestingly, the observed effects of administered E on COMT gene expression suggest an enhancement of its own catabolism or, reciprocally, a stimulation morphine biosynthesis.

Dopamine is a requisite intermediate precursor molecule in the morphine biosynthetic pathway [13, 19, 31]. The intimate and interactive coupling of "morphinergic" to dopaminergic behavioral processes provide a cogent window of under-standing additive behavioral processes. For example, initial speculation 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 opiate abuse, who advanced the hypothesis that the reinforcing or additive effects of ethanol were functionally linked to the cellular effects of DA derived isoquinoline alkaloids, notably the tetrahydroisoquinoline salsolinol [32-34] and the benzylisoquinoline morphine precursor tetra-hydropapaveroline (THP) [35-37]. Recognition of tetra-hydroisoquinolines, THP, and endogenous mor-phine as active principles of alcohol abuse was inherently linked to their normal presence in dopaminergic neurons, enhanced cellular expression following chronic ethanol intake [37-42], and concentration-dependent disregulation of DA metabolism and/or dopaminergic signaling in mesolimbic/mesocortical areas such as the nucleus accumbens and the ventral tegmental area traditionally associated with reward and reinforcement of ethanol intake [15, 16, 43-51]. The causal relationship and functional association of CNS expression of tetrahydroisoquinoline and benzy-lisoquinoline alkaloids to alcohol abuse remains controversial despite anatomical, physiological, pharmacological, and behavioral evidence linking dopaminergic and opioidergic systems in limbic areas associated with reinforcement of ethanol intake behaviors [17, 21, 52-56].

This link is equally important when considering animal behavior. It can be surmised that the DA component modulates excitatory states, including rage, whereas the morphinergic component offers calming action associated with relaxation and reward. This association may also explain the calming effect following excitatory emotional states. Moreover, in this scenario of DA synthesis coming before that of morphine one would predict excitation would precede the calm, which may be associated with morphine signaling. Furthermore, this coupling may also explain the fact that within various relaxation techniques an excitatory stress component emerges physiologically before relaxation sets in [21-23, 48, 57]. The link between catecholamine and morphine metabolism promises to be the subject of future investigations given its significance in biomedicine. This link is critical in offering a novel explanation for idiopathic hypertension via identification of physiological deficits in vascular endothelial "morphinergic"/NO/catecholamine-coupled signaling events. Investigation of the potential involvement of COMT and its genetic polymorphisms in metabolic/pathophysiological states represents an area for intense biomedical research advancement.

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