Catechol-O-methyltransferase: potential relationship to idiopathic hypertension

Kirk J. Mantione, Richard M. Kream, George B. Stefano

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 μ3 and μ4 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, μ3 and μ4 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 μ3 and μ4 opiate receptors [1, 6], and several human cancer cell lines [1, 2, 5, 7, 8]. We have therefore hypothesized that μ3 and μ4 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 μ3/μ4 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 tetrahydropapaveroline (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 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 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

\[ DBH + PNMT = \text{epinephrine} \]

\[ \text{Dopamine} + \text{CYP2D6, PNMT} + \text{COMT} = \text{codeine then morphine} \]

**Figure 1.** Human vascular endothelial cells contain the μ3/μ4 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 colon adenocarcinoma 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 understanding 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 tetrahydroisoquinoline salsolinol [35-37]. Recognition of tetrahydroisoquinolines, THP, and endogenous morphine 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 benzylisoquinoline 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.

References

1. Cadet P, Mantione KJ, Stefano GB. Molecular identification and functional expression of mu3, a novel alternatively spliced variant of the human mu opiate receptor gene. J Immunol 2003; 170: 5118-23.
2. Zhu W, Cadet P, Baggerman G, Mantione KJ, Stefano GB. Human white blood cells synthesize morphine: CYP2D6 modulation. J Immunol 2005; 175: 7357-62.
3. Stefano GB, Hartman A, Bilfinger TV, et al. Presence of the mu3 opiate receptor in endothelial cells: coupling to nitric oxide production and vasodilation. J Biol Chem 1995; 270: 30290-3.
4. Cadet P, Bilfinger TV, Fimiani C, Peter D, Stefano GB. Human vascular and cardiac endothelia express mu opiate receptor transcripts. Endothelium 2000; 7: 185-91.
5. Zhu W, Bilfinger TV, Baggerman G, Goumon Y, Stefano GB. Presence of endogenous morphine and morphine 6 glucuronide in human heart tissue. Int J Mol Med 2001; 7: 419-22.
6. Cadet P, Mantione K, Bilfinger TV, Stefano GB. Real-time RT-PCR measurement of the modulation of Mu opiate receptor expression by nitric oxide in human monocellular cells. Med Sci Monit 2001; 7: 1123-8.
7. Boettcher C, Fellermeier M, Boettcher C, Drager B, Zenk MH. How human neuroblastoma cells make morphine. Proc Natl Acad Sci U S A 2005; 102: 8495-500.
8. Pfeaknapa C, Schmidt I, Brandsch M, Dräger B, Zenk MH. Endogenous formation of morphine in human cells. Proc Nat Acad Sci U S A 2004; 101: 14091-6.
9. Brix-Christensen V, Tonnesen E, Sanchez RG, Bilfinger TV, Stefano GB. Endogenous morphine levels increase following cardiac surgery as part of the antiinflammatory response? Int J Cardiol 1997; 62: 191-7.
10. Liu Y, Bilfinger TV, Stefano GB. A rapid and sensitive quantitation method of endogenous morphine in human plasma. Life Sci 1996; 60: 237-43.
11. Bilfinger TV, Kushnerik V, Bundz S, Liu Y, Stefano GB. Evidence for dopamine downregulating immunocytes during cardiopulmonary bypass in a porcine model. Int J Cardiol 1996; 53: S39-46.

12. Cadet P, Mantione KJ, Zhu W, Kream RM, Sheehan M, Stefano GB. A functionally coupled mu3-like opiate receptor/nitric oxide regulatory pathway in human multi-lineage progenitor cells. J Immunol 2007; 179: 5839-44.

13. Kream RM, Stefano GB. De novo biosynthesis of morphine in animal cells: an evidence-based model. Med Sci Monit 2006; 12: RA207-19.

14. Fricchione G, Zhu W, Cadet P, et al. Identification of endogenous morphine and a mu3-like opiate receptor in human brain tissue taken from a patient with intractable complex partial epilepsy. Med Sci Monit 2008; 14: CS45-9.

15. Kream RM, Stefano GB. Homeopathic ethanol. Med Sci Monit 2008; 14: SC11-3.

16. Mantione KJ, Cadet P, Zhu W, et al. Endogenous morphine signaling via nitric oxide regulates the expression of CYP2D6 and COMT: autocrine/paracrine feedback inhibition. Addict Biol 2008; 13: 118-23.

17. Stefano GB, Stefano JM, Esch T. Anticipatory stress response: a significant commonality in stress, relaxation, pleasure and love responses. Med Sci Monit 2008; 14: RA17-21.

18. Zhu W, Esch T, Kream RM, Stefano GB. Converging cellular processes for substances of abuse: endogenous morphine. Neuro Endocrinol Lett 2008; 29: 63-6.

19. Stefano GB, Kream RM. Endogenous morphine synthetic pathway preceded and gave rise to catecholamine synthesis in evolution. Int J Mol Med 2007; 20: 837-41.

20. Haavik J, Blau N, Thony B. Mutations in human monoamine-related neurotransmitter pathway genes. Hum Mutat 2008; 29: 891-902.

21. Kream RM, Stefano GB. Endogenous morphine and nitric oxide coupled regulation of mitochondrial processes. Med Sci Monit 2009; 15: RA263-8.

22. Stefano GB, Esch T, Kream RM. Xenobiotic perturbation of endogenous morphine signaling: paradoxical opiate hyperalgesia. Med Sci Monit 2009; 15: RA107-10.

23. Stefano GB, Kream RM, Esch T. Revisiting tolerance from the endogenous morphine perspective. Med Sci Monit 2009; 15: RA189-98.

24. Zhu W, Stefano GB. Comparative aspects of endogenous morphine synthesis and signaling in animals. Ann N Y Acad Sci 2009; 1163: 330-9.

25. Gu Y, Yuen L, Tian Y; Hu Z. Association between COMT gene and Chinese male schizophrenic patients with violent behavior. Med Sci Monit 2009; 15: CR848-9.

26. Syvanen AC, Tilgmann C, Rinne J, Ulmanen I. Genetic polymorphism of catechol-O-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics 1997; 7: 65-71.

27. Lachman HM. Does COMT val158met affect behavioral phenotypes: yes, no, maybe? Neuropsychopharmacology 2009; 34: 1030-4.

28. Duncan CC, Fernando PW. Effects of tetrahydrodiproisoquinolines in the nucleus accumbens and the ventral tegmental area on ethanol preference in the rat. Alcohol 1991; 8: 87-90.

29. Myers RD. Anatomical “circuitry” in the brain mediating alcohol drinking revealed by THP-reactive sites in the limbic system. Alcohol 1999; 7: 449-59.

30. Myers RD, Robinson DE. Tetrahydrodiproisoquinoline injected in the ventral tegmental area shifts dopamine efflux differentially in the shell and core of nucleus accumbens in high-ethanol-prefering (HEP) rats. Alcohol 1999; 18: 83-90.

31. Sallstrom BS, Hill R, Kianmamaa K, Rommelspacher H. Effect of ethanol on (R)- and (S)-salsolinol, salsoline, and THP in the nucleus accumbens of AA and ANA rats. Alcohol 1999; 18: 165-9.

32. Esch T, Stefano GB. The neurobiology of stress management. Neuro Endocrinol Lett 2010; 31: 30.

33. Myers RD, Robinson DE. Tetrahydrodiproisoquinoline injected in the ventral tegmental area shifts dopamine efflux differentially in the shell and core of nucleus accumbens in high-ethanol-prefering (HEP) rats. Alcohol 1999; 18: 83-90.

34. Yu G, Yuen L, Tian Y; Hu Z. Association between COMT gene and Chinese male schizophrenic patients with violent behavior. Med Sci Monit 2009; 15: CR848-9.

35. Syvanen AC, Tilgmann C, Rinne J, Ulmanen I. Genetic polymorphism of catechol-O-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics 1997; 7: 65-71.

36. Lachman HM. Does COMT val158met affect behavioral phenotypes: yes, no, maybe? Neuropsychopharmacology 2009; 34: 1030-4.
50. Roy JR, Chakraborty S, Chakraborty TR. Estrogen-like endocrine disrupting chemicals affecting puberty in humans – a review. Med Sci Monit 2009; 15: RA137-45.
51. Atmanene C, Laux A, Glattard E, et al. Characterization of human and bovine phosphatidylethanolamine-binding protein (PEBP/RKIP) interactions with morphine and morphine-glucuronides determined by noncovalent mass spectrometry. Med Sci Monit 2009; 15: BR178-87.
52. Haber H, Roske I, Rottmann M, Georgi M, Melzig MF. Alcohol induces formation of morphine precursors in the striatum of rats. Life Sci 1997; 60: 79-89.
53. McCoy JG, Strawbridge C, McMurtrey KD, Kane VB, Ward CP. A re-evaluation of the role of tetrahydropapaveroline in ethanol consumption in rats. Brain Res Bull 2003; 60: 59-65.
54. Naoi M, Maruyama W, Nagy GM. Dopamine-derived salsolinol derivatives as endogenous monoamine oxidase inhibitors: occurrence, metabolism and function in human brains. Neurotoxicology 2004; 25: 193-204.
55. Shearman GT, Herz A. Ethanol and tetrahydroisoquinoline alkaloids do not produce narcotic discriminative stimulus effects. Psychopharmacology (Berl) 1983; 81: 224-7.
56. Santamaria F, De SS, Montella S, et al. Nasal nitric oxide assessment in primary ciliary dyskinesia using aspiration, exhalation, and humming. Med Sci Monit 2008; 14: CR80-5.
57. Stefano GB, Fricchione GL, Slingsby BT, Benson H. The placebo effect and relaxation response: neural processes and their coupling to constitutive nitric oxide. Brain Res Rev 2001; 35: 1-19.