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Homeopathic ethanol

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Summary

Ethanol has had a long and deep association with the historical development of world culture. Ostensibly, its consumption has both short and long term positive and negative effects, based on moderate or excessive intake, respectively. The predominant thrust of empirical research, however, into the multiple biological effects of ethanol has led to its negative designation as a major addictive substance. Multiple lines of research have elucidated functional interactions of ethanol in opioid modulation of dopaminergic transmission in CNS reward systems. In parallel, recent work has demonstrated that animal cells have the ability to effect *de novo* synthesis of chemically authentic morphine from dopamine (DA) and DA-related aromatic precursor molecules. Interestingly, we have observed that sub-threshold concentrations of ethanol alter cellular distributions of endogenously expressed morphine. Reciprocal autocrine/paracrine modulatory effects of very low concentrations of morphine in concert with ethanol also suggest the potential for endogenous expression and action of homeopathic concentrations of ethanol within discrete cellular microdomains. Perturbation of this subtle regulatory relationship by exogenous intake of ethanol may shed light on the biochemical and molecular bases of reward and addictive states.

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endogenous morphine • ethanol • alcohol • dopamine • health

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Ethanol consumption has been identified as a prime motivational and integrative principle positively linked to developmental processes throughout world cultural history [1]. In contrast, the predominant thrust of empirical research into multiple biological effects of ethanol have led to its negative designation as a major addictive substance [2–16]. Accordingly, there has been a dearth of empirical studies designed to elucidate the physiological roles of ethanol in maintaining positive cellular homeostasis in biological systems [17–19].

The functional interaction of ethanol in opioid modulation of dopaminergic transmission in well-established CNS reward systems has been documented [20–24] with a convergence of effect on dopamine [25–28], specifically on mesocortical-mesolimbic A10 dopamine (DA) neurons [29–35]. Recent reports for our laboratory and those of other investigators demonstrated that animal cells have the ability to effect *de novo* synthesis of chemically authentic morphine from DA and additional tyrosine-related aromatic precursor molecules [36,37]. The cellular expression of endogenous morphine is intimately associated with co-expression of its cognate μ 3 opiate receptor, a G protein coupled membrane protein highly selective for morphinan-related opiate alkaloids and unresponsive to opioid peptides [38].

The ability of 1% ethanol to effectively enhance cellular levels of endogenous morphine may be functionally linked to its anesthetic properties at higher concentrations [39]. Because DA and its immediate precursors tyrosine, dihydroxyphenylalanine (DOPA), and tyramine also serve as biosynthetic intermediates in cellular morphine expression [36,37], ethanol-mediated anesthetic inhibition of dopamine signaling may effectively divert excess precursor molecules to cellular morphine pools.

A recent novel observation functionally links concentration-dependent effects of ethanol to different biochemical processes in invertebrate nervous tissues from *Mytilus edulis* pedal ganglia. A very high concentration of 200 mM or 1% ethanol, known to produce severe CNS respiratory depression in higher organisms, is observed to promote accumulation of cellular morphine in *M. edulis* ganglia [40,41], whereas a 100 fold lower concentration of 2 mM ethanol, equivalent to a non-activating, sensitizing, dose of 0.01% is observed to produce an effective doubling of 125 I-trace labeled morphine released into the extracellular medium. Furthermore, a recent publication has attributed sensitizing effects of low concentrations of ethanol to activation of endogenous opioid systems [42].

Our demonstration that non-activating, sensitizing, doses of 0.01% ethanol are capable of promoting endogenous morphine release may have profound implications for understanding polymodal addictive processes involving a variety of drugs of abuse, including alcohol. Importantly, a basic regulatory relationship is suggested whereby sub-threshold concentrations of ethanol and endogenously expressed morphine mediate local circuit modulation of DA-ergic actions. Reciprocal autocrine/paracrine modulatory effects of very low concentrations of morphine in concert with ethanol also suggest the potential for endogenous expression and action of homeopathic concentrations of ethanol within discrete cellular microdomains.

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