# Multi-author Review

# Molecular mechanisms of intracellular ethanol action

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## Introduction

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Prior to the early 1970's, the accepted scientific view of the effect of ethanol on the central nervous system was that it altered neuronal activity by virtue of a non-specific interaction with neuronal membranes, rather than through an induced receptor-mediated mechanism.

During the 1970's, as knowledge of the molecular structure and function of the nervous system began to be more clearly understood, the role of neurotransmitters and neuromodulators, the actions at the synapse, and the role of receptor-mediated coupling events triggering second messenger activity began to be revealed.

Scientists have identified endogenous neuropeptides such as the opioids and their respective receptors, the endogenous receptors and functional pathways for certain neurotransmitter systems (i.e., serotonergic, adrenergic, cholinergic, and GABAergic), and certain neuronal intracellular signalling mechanisms and metabolic substrates. Progress is also being made in clarifying the role of molecular genetics in neurophysiological processing.

Such findings have provided powerful new tools for the systematic investigation of the molecular mechanisms involved in the intracellular actions of ethanol. We have learned that alcohol affects neuronal membrane fluidization; alters certain endogenous receptor activity; modifies the biosynthetic pathways of biogenic amines and neuropeptides; induces neuronal adaptive responses; affects neuronal conductance and second messenger responses; and that the pharmacological response to alcohol is controlled in part by genetic mechanisms.

This extensive research, in addition to providing new insights, has posed several controversial questions: How does ethanol affect intracellular neuronal mechanisms? What are the biosynthetic and regulatory processes of the neurotransmitters and neuromodulators, and their receptors, that are affected by ethanol? What are the neurogenetic and molecular components of the etiology of alcoholism?

The papers below address essential aspects of these questions:

Gandhi and Ross describe experiments which substantiate the differential effects of ethanol on calcium and inositol phospholipids on second messenger mechanisms. The authors show that increased sensitivity of three calcium-dependent processes during chronic ethanol exposure involves coupling of one or more of these processes to receptor-mediated events, and may provide the molecular basis for ethanol-induced adaptation.

Gianoulakis shows through experimental evidence that ethanol significantly influences the release, biosynthesis, and post-translational processing of the opioid peptides. She describes how ethanol modifies the function of central opiate receptors, and discusses the possible involvement of the opioid peptides (for example, $\beta$-endorphin) in the genetic predisposition to alcoholism.

Charness points out that ethanol may modulate endogenous opioid systems by disrupting opioid receptor signalling. Utilizing experiments involving neuronal cell lines, he shows that ethanol affects both $\mu$- and $\delta$-opioid receptors differentially, and suggests that protein synthesis is involved in adaptive changes. In certain cell lines exposed to ethanol, up-regulation of the $\delta$-opioid receptor renders these cells 3.5-fold more sensitive to opioid inhibition of adenylyl cyclase.

Ticku suggests, based upon recent experimental data, that ethanol, similar to drugs such as benzodiazepines and barbiturates, enhances GABAergic transmission in mammalian CNS. One mechanism for such enhancement involves augmentation of GABA-induced Cl-fluxes by ethanol. These enhancing effects of ethanol are shown by Ticku to be blocked by GABA antagonists, and by the classical benzodiazepine azido analog Ro15-4513.

Myers discusses the extensive literature which supports the formation and sequestration of amine-aldehyde adducts, the tetrahydro-isoquinoline (TIQ) and $\beta$-carboline (THBC) compounds, following alcohol consumption in both alcoholics and non-alcoholics. Based on laboratory investigations, he describes evidence which implicates these condensation products as mediators of addictive drinking of alcohol. Furthermore, based on a series of experiments, he proposes that the abnormal intake of alcohol is related functionally to opioid and dopaminergic mechanisms in the brain.

Blum and colleagues propose that uncontrollable alcohol ingestive behavior is linked to a deficit of dopaminergic and serotonergic neurotransmission, primarily in the meso-limbic region-hypothalamic axis. They point out that, based on experimental evidence, that ethanol ingestive behavior is a function of photoperiod, and involves alterations in both pineal and hypothalamic opioid peptides. Not only are these findings relevant to human alcoholism, they are also important in furthering our understanding of the neuromechanisms involved in other forms of behavior.

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