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SCIENCE DIRECT
Pharmacology & Therapeutics 111 (2006) 533 – 554
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: A.L. Morrow

Ethanol modulation of GABAergic transmission: The view from the slice

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Abstract

For almost three decades now, the GABAergic synapse has been the focus of intense study for its putative role in mediating many of the behavioral consequences associated with acute and chronic ethanol exposure. Although it was initially thought that ethanol interacted solely with the postsynaptic $GABA_A$ receptors that mediate the majority of fast synaptic inhibition in the mammalian central nervous system (CNS), a number of recent studies have identified novel pre- and postsynaptic mechanisms that may contribute to the acute and long-term effects of ethanol on GABAergic synaptic inhibition. These mechanisms appear to differ in a brain region specific manner and may also be influenced by a variety of endogenous neuromodulatory factors. This article provides a focused review of recent evidence, primarily from in vitro brain slice electrophysiological studies, that offers new insight into the mechanisms through which acute and chronic ethanol exposures modulate the activity of GABAergic synapses. The implications of these new mechanistic insights to our understanding of the behavioral and cognitive effects of ethanol are also discussed.

Keywords: GABA; Ethanol; Electrophysiology; Presynaptic; Postsynaptic

Abbreviations: AMPA, α-amino-3-hydroxi-5-methylisoxazole-4-propionic acid; BZP, benzodiazepine; CeA, central nucleus of the amygdala; CIE, chronic intermittent ethanol; CNS, central nervous system; CRF, corticotrophin releasing factor; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; GDP, giant depolarizing potential; IPSC, inhibitory postsynaptic current; IPSP, inhibitory postsynaptic potential; NMDA, *N*-methyl-D-aspartate; PKA, protein kinase A; PKC, protein kinase C; PPD, paired-pulse depression; PPF, paired-pulse facilitation; TTX, tetrodotoxin; VGCC, voltage-gated calcium channel; VTA, ventral tegmental area.

Contents

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0163-7258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2005.11.002

1. Introduction

γ-Aminobutyric acid (GABA) was first identified over three decades ago as the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) (Bloom & Iversen, 1971). Almost immediately following those pioneering studies, reports began to emerge suggesting that the acute behavioral and cognitive effects of ethanol were mediated in part via an enhancement of GABAergic inhibition (e.g., Davidoff, 1973; Nestoros, 1980). In the coming years, numerous studies, employing a variety of behavioral, neurochemical, and electrophysiological approaches provided additional support for this hypothesis (for detailed, historical reviews of these studies, see Deitrich et al., 1989; Criswell & Breese, 2005).

The first mechanistic theories centered on the idea that ethanol enhanced synaptic inhibition primarily via a direct allosteric facilitation of the activity of $GABA_A$ receptors, which mediate the vast majority of fast synaptic inhibition in the mammalian CNS. These theories were based initially on observations from numerous behavioral studies, which noted that ethanol shared many of the sedative, anxiolytic, and anticonvulsant properties of drugs known to enhance $GABA_A$ receptor function (e.g., benzodiazepines [BZPs] and barbiturates; Deitrich et al., 1989) and that cross-tolerance could develop between ethanol and drugs that enhance $GABA_A$ receptor activity (Le et al., 1986; Mihic et al., 1992). Moreover, $GABA_A$ receptor agonists or drugs that raise endogenous levels of GABA were shown to potentiate the sedative, hypnotic, ataxic, and anticonvulsant actions of ethanol (Hakkinen & Kulonen, 1976; Frye & Breese, 1982; Liljequist & Engel, 1982; Martz et al., 1983), whereas $GABA_A$ receptor antagonists and certain benzodiazepine partial inverse agonists (Ro 45-1513) could reduce some of the intoxicating effects of ethanol (Hakkinen & Kulonen, 1976; Liljequist & Engel, 1982; Martz et al., 1983; Suzdak et al., 1986b). The findings that a range of allosteric $GABA_A$ receptor modulators could substitute for ethanol in drug discrimination studies (Kline & Young, 1986; Barry, 1991; Ator et al., 1993; Hodge & Alken, 1996) provided further support for this theory.

While the evidence from most behavioral studies supported the idea that ethanol enhanced GABAergic inhibition via an allosteric facilitation of $GABA_A$ receptor function, direct biochemical and/or electrophysiological evidence in support of such a mechanism proved surprisingly elusive. Although initial neurochemical (Suzdak et al., 1986a; Morrow et al., 1988) and electrophysiological (Aguayo, 1990; Reynolds & Prasad, 1991) studies seemed to suggest that pharmacologically relevant concentrations of ethanol could exert an allosteric facilitation of $GABA_A$ receptor function, these effects were often quite variable (Reynolds et al., 1992) and in some cases not observed (Osmanovic & Shefner, 1990; White et al., 1990; Mihic et al., 1991). Notably, evidence from in vitro studies investigating ethanol effects on GABAergic synaptic transmission also proved highly variable (see Section 3).

Over the last decade or so, a variety of methodological advances have greatly facilitated the study of the physiological and pharmacological properties of synapses in in vitro brain slice preparations. Numerous ethanol researchers have employed these improved methods to reexamine the acute effects of ethanol on GABAergic neurotransmission in a number of brain regions and in a variety of species from mouse to monkey. These recent studies have shed new light on the complexity surrounding the interaction between ethanol and the GABAergic synapse. While the majority of these studies have now provided compelling evidence that ethanol can indeed enhance GABAergic synaptic activity, these studies also suggest that the mechanisms underlying this enhancement are far more complex than initially appreciated and often involve interplay between both pre- and postsynaptic mechanisms.

The purpose of this article is to provide a highly focused overview of the findings of studies from the past decade or so that offer novel insight into specific pre- and postsynaptic mechanisms through which ethanol enhances GABAergic neurotransmission in the mammalian CNS. The focus will be mainly to examine this interaction from the perspective of native receptors in tissue slices with an emphasis on electrophysiological studies. The implications of these new mechanistic insights to our understanding of the behavioral and cognitive effects of ethanol and the treatment of alcohol-related disorders will also be discussed. Other aspects regarding the interaction of ethanol with GABAergic transmission and GABA receptors have been reviewed elsewhere (Macdonald, 1995; Klein & Harris, 1996; Mihic, 1999; Aguayo et al., 2002; Boehm et al., 2004; Kumar et al., 2004; Criswell & Breese, 2005).