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Anesthetic effects changeable in habitual drinkers: Mechanistic drug interactions with neuro-active indoleamine–aldehyde condensation products associated with alcoholic beverage consumption

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ABSTRACT

Clinicians often experience the reduced efficacy of general and local anesthetics and anesthesia-related drugs in habitual drinkers and chronic alcoholics. However, the mechanistic background underlying such anesthetic tolerance remains unclear. Biogenic indoleamines condense with alcohol-derived aldehydes during fermentation processes and under physiological conditions to produce neuro-active tetrahydro-β-carbolines and β-carbolines, many of which are contained not only in various alcoholic beverages but also in human tissues and body fluids. These indoleamine–aldehyde condensation products are increased in the human body because of their exogenous and endogenous supply enhanced by alcoholic beverage consumption. Since tetrahydro-β-carbolines and β-carbolines target receptors, ion channels and neuronal membranes which are common to anesthetic agents, we propose a hypothesis that they may pharmacodynamically interact at $GABA_A$ receptors, NMDA receptors, voltage-gated Na^+ channels and membrane lipid bilayers to attenuate anesthetics-induced positive allosteric $GABA_A$ receptor modulation, NMDA receptor antagonism, ion channel blockade and neuronal membrane modification, thereby affecting anesthetic efficacy. The condensation products may also cooperatively interact with ethanol that induces adaptive changes and cross-tolerance to anesthetics and with dopamine–aldehyde adducts that act on $GABA_A$ receptors and membrane lipids. Because tetrahydro-β-carbolines and β-carbolines are metabolized to lose or decrease their neuro-activities, induction of the relevant enzymes by habitual drinking could produce an inter-individual difference of drinkers in susceptibility to anesthetic agents. The present hypothesis would also provide a unified framework for different modes of anesthetic action, which are inhibited by neuro-active indoleamine–aldehyde condensation products associated with alcoholic beverage consumption.

Introduction

Alcohol drinking is linked to a negative influence on different classes of drugs to act in the central and peripheral nervous system. Clinicians often experience the reduced efficacy of anesthetics and anesthesia-related drugs (sedatives, antinociceptives and anesthetic adjuncts) in habitual drinkers or more difficult anesthesia of alcoholics compared with non-alcoholic patients. Long-term alcohol intake and chronic alcoholism make experimental animals and humans less susceptible to general anesthetics, resulting in an increase of doses required for successful anesthesia induction, sensory block, loss of consciousness and anesthesia maintenance. Repeated alcohol administration and habitual drinking change the effects of intravenous anesthetics like barbiturates, benzodiazepines and propofol [1,2] and inhalational anesthetics like isoflurane and nitrous oxide [3,4]. The responses to ketamine of alcohol-dependent patients are different from those of healthy subjects [5]. Such anesthetic tolerance also develops in local anesthetics. The anesthetic effect and duration of lidocaine are limited by chronic alcohol administration [6]. It is generally difficult for dental patients with the history of habitual drinking to achieve satisfactory pain control with local anesthetics [7,8].

Drug tolerance or reduced drug efficacy is generally interpreted by pharmacokinetic changes of drug metabolism and distribution and pharmacodynamic changes of drug-acting site and pharmacological potency. Chronic alcohol administration was suggested to enhance the clearance of barbiturates in humans and rats through promotion of their metabolism [9]. However, experimental alcohol intake did not induce a metabolic enzyme for thiopental [10] nor decrease a blood concentration of propofol [2]. In rats chronically

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administered with alcohol, the increased liver solubility was reported for isoflurane, enflurane, halothane and methoxyflurane [11]. While many cells alter the sensitivity, infiltrative property and metabolic activity by adaptation to ethanol exposure, brain synaptosomal membranes and liver mitochondrial membranes become resistant to halothane and phenobarbital in rats and mice [12]. Although alcohol may possibly induce the metabolic acidosis to decrease the diffusion of anesthetic molecules through nerve sheaths or into neuronal membranes and the regional vasodilation to carry away anesthetic molecules from the injection site, such possibilities do not apply to local anesthetics [13,14].

Besides ethanol to influence anesthetic susceptibility, other biomolecules closely related to drinking behaviors are contributable to the development of anesthetic tolerance. We propose a hypothetical mechanism that neuro-active compounds increasingly produced by consuming alcoholic beverages may cause the pharmacodynamic interactions with general and local anesthetics at receptors, ion channels and neuronal membranes which are the common targets of anesthetic agents.

Hypothesis

Aldehydes (acetaldehyde and formaldehyde) derived from alcohols non-enzymatically condense with biogenic indoleamines (tryptamine and serotonin) to form a series of compounds with a common structure of 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, called tetrahydro-β-carbolines, which are further oxidized to β-carbolines. Such condensation products and their derivatives include tetrahydroharman, tetrahydronorharman, tetrahydroharmanol, harman, norharman, harmaline, harmine, etc. Although they were originally found in some plant species (*Peganum harmala* and *Passiflora incarnata*) as alkaloid components, they are also present in various alcoholic beverages and in human tissues and body fluids because the condensation reaction easily occurs during fermentation processes and under physiological conditions [15,16]. Tetrahydroharman, tetrahydronorharman and their related β-carbolines are significantly increased in the human body through drinking behaviors to promote their exogenous supply and endogenous production [17,18]. Since the indoleamine–aldehyde condensation products target functional proteins and membrane lipids which are common to general anesthetics and local anesthetics, they may at least partly relate to the unsuccessful anesthesia associated with alcoholic beverage consumption. Neuro-active tetrahydro-β-carbolines and β-carbolines increased by habitual drinking are hypothesized to interact with anesthetics and anesthesia-related drugs at $GABA_A$ receptors, NMDA receptors, ion channels and membrane lipid bilayers (Fig. 1). Such pharmacodynamic interactions would affect the effects of anesthetic agents by attenuating their induced positive allosteric $GABA_A$ modulation, NMDA receptor antagonism, voltage-gated Na^+ channel blockade and neuronal membrane modification.

Discussion

Different modes of action of anesthetic agents

Although anesthesia was discovered over 150 years ago, the defined site of action and the detailed molecular mechanism have been still arguable about general and local anesthetics. Their pharmacological targets are referred to as functional proteins (receptors and ion channels) in the protein theory and as membrane lipids (neuronal membrane-constituting lipid bilayers) in the lipid theory.

Intravenous anesthetics, volatile anesthetics and sedatives primarily target ligand-gated ion channels, $GABA_A$ receptors and NMDA receptors [19]. While inhibitory $GABA_A$ receptors are most abundantly found throughout the mammalian central nervous system, general anesthetics and anesthesia-related drugs including

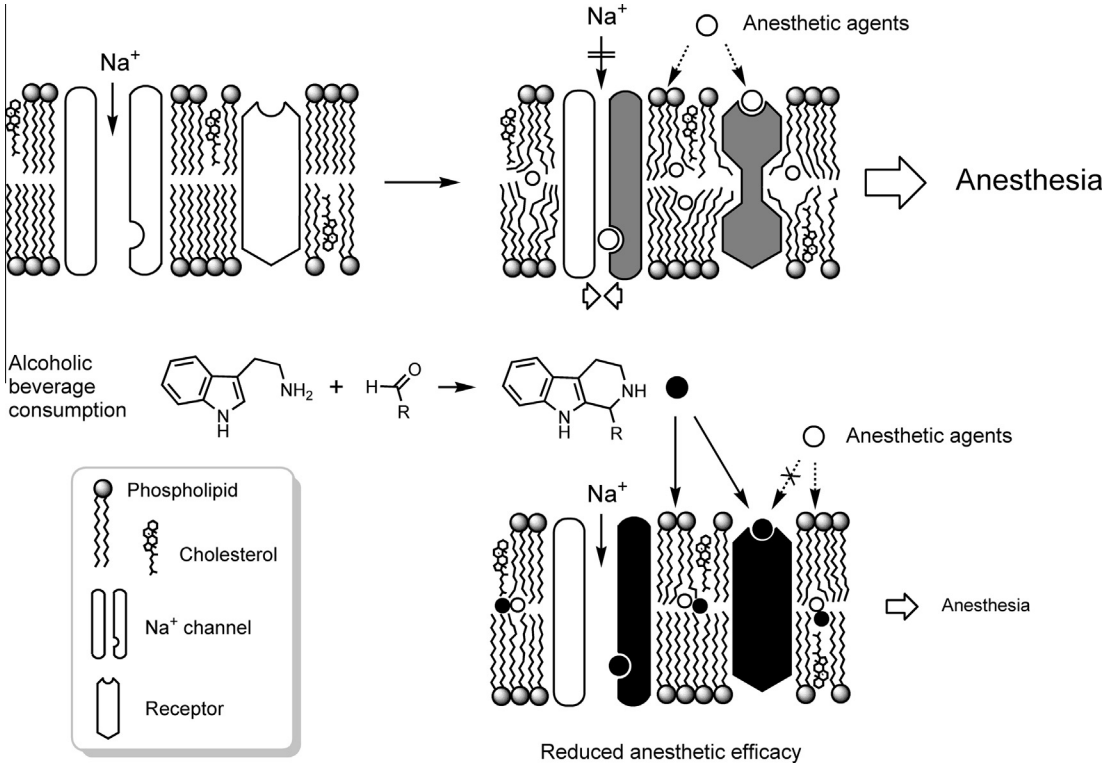

Fig. 1. Neuro-active indoleamine–aldehyde condensation products (represented by tetrahydro-β-carboline), which are increased in the human body by consuming alcoholic beverages, may interact with anesthetic agents at receptors, ion channels and neuronal membranes to reduce their efficacy.