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Euphoria from drinking alcoholic beverages may be due to reversible constriction of cerebral blood vessels: potential roles of unrecognized ionized hypomagnesemia, and release of ceramides and platelet-activating factor

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Euphoria is an affective state and a form of pleasure that goes back to biblical times. It makes a person experience intense forms of well-being, happiness, and often ecstasy. It has often been suggested that euphoria induced by alcohol and other drugs/compounds (e.g., psychoactive drugs, designer drugs, stimulants, nicotine, gamma-hydroxybutyric acid, ketamine, etc.) occurs *via* a stimulation of all hedonic hotspots within the brain's reward system [1]. Interestingly, asphyxiation initially produces an intense feeling of euphoria, often leading people to intentionally induce asphyxiation and erotic sensations (*i.e.*, brief episodes of hypoxia such as choking).

More than 35 years ago, three of us, using a TV-image-intensification recording system, at magnifications up to 3,200 times (pioneered by our lab) [2] and using *in-vivo* examination of the living brain microcirculation in different anesthetized rodents (*i.e.*, rats, mice, guinea-pigs) reported that very small amounts of alcohol (equivalent to one-two drinks) reversibly constricted arterioles (20-40 μm in diameter) and muscular venules (40-75 μm in diameter) [3]. These initial findings suggested to us that the amount of alcohol in only two cocktail drinks may be enough to curtail blood flow in the brain to the point that some key neurons, glial cells, and astrocytes do not get enough oxygen to function properly. We suggested, like that seen in pilots at high altitude (> 15,000 feet) in non-pressurized cabins, in World War II, who experienced a euphoric sense of well-being, drinking of alcohol and the taking of diverse psychoactive/designer drugs can reversibly induce vasoconstriction of the cerebral microscopic blood vessels, thus producing oxygen-lack and temporary light-headedness and euphoria. The neurons, glial cells, and astrocytes in select areas of the brain would thus be starved for oxygen like unprotected pilots at high-altitude. Until the advent of pressurized cabins, many pilots in World War II became very euphoric, blacked out, lost control of their aircraft and perished.

Using isolated arteries from brains of anesthetized, sacrificed rats, guinea-pigs, dogs, and subhuman primates, bathed in physiological salt solutions, our laboratories found that various alcohols (*i.e.*, ethanol, methanol, and butanol) caused concentration-dependent contractions, similar to the *in-vivo* studies on the living brains of rodents [3-15]. The greater the dose of alcohol, the greater the vasoconstrictor-contraction effects and the longer the contractions remain unabated [3-16]. Such

effects clearly could be the cause of the sequelae of effects noted with increased consumption of cocktails, beers, and various liquors, *i.e.*, the failure to be able to walk a straight line, the failure to drive a vehicle safely, unconsciousness, coma and in rare cases strokes and death [3,7-16]. Drinking of alcohol thus can be, and often is, lethal. In fact, drinking of alcohol is the most abused type of drug/behavior [1,17,18]. Other experiments from our group have shown that hallucinogenic drugs such as LSD, phencyclidine (PCP, "angel dust"), psilocybin, mescaline, heroin, pyote, cocaine, excitatory amino acids and derivatives (*i.e.*, designer drugs) also promote vasoconstriction of brain blood vessels [19-27]. The concentrations of PCP, mescaline, LSD and cocaine that produced near maximum and intense euphoria, often leading to death, were similar to the concentrations in the blood and brains of humans who had died from overdoses of PCP, LSD, and mescaline.

Using rats addicted to ethanol, we found that the *in-situ* cerebral micro vessels as well as cerebral and peripheral arteries (removed from the addicted animals) gradually, with the passage of time (and increased blood alcohol levels), became tolerant to the alcohol [8,10,14, unpublished findings]. In other words, it takes higher and higher concentrations of alcohol to induce microvascular contractions, which would thus produce a need for increased blood alcohol levels in order to induce euphoric states, exactly as occurs in humans with increased drinking. Breathing is controlled by the brain. Cutting off the blood supply to the neurons, etc., that regulate breathing may produce euphoria at very low concentrations of alcohol and hallucinations at higher blood levels of alcohol.

What, however, is the exact mechanism(s) which induce euphoria and hallucinations via a reduced cerebral vascular blood and oxygen supply? Until now, speculation resided in a release of endorphins,

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gamma-hydroxybutyric acid-like substances, and a variety of putative neurotransmitters [14,15,17,18]. However, none of these substances and multiple transmitters (e.g., norepinephrine, dopamine, serotonin, histamine, prostanoids, neuropeptides, glutamic acid, etc.) that we [13-17, 28-31; unpublished studies on microvasculatures of rodent brains] and others have tested [32] produce ischemic actions in the brain microvasculature at blood levels found to be released with imbibing of alcohol.

We now believe that a rapid, reversible release of free magnesium ions ($[Mg^{2+}]$) coupled to the release of ceramides and platelet-activating factor (PAF) may account for most of the alcohol-induced euphoria. Below, we discuss why this hypothesis looks tenable to us.

Many drugs including alcohol are now known to induce reversible Mg^{2+} deficiency in organs, tissues, and cells in both animals and humans. Flink and his co-workers in 1954 were the first to demonstrate severe hypomagnesemia in alcoholic patients [33]. Over the succeeding years these findings have been confirmed and extended by others [34]. In fact, infusions of magnesium sulfate have been standard treatment of delirium tremens for a good number of years. Approximately 25 years ago, our group, for the first time, employing ^{31}P -nuclear magnetic resonance (^{31}P -NMR) spectroscopy and optical spectroscopy on the living intact brains of animals as well as utilization of digital-imaging microscopy on a variety of isolated cerebral vascular smooth muscle (VSM) cells, and use of highly-specific Mg^{2+} electrodes, found that alcohol rapidly (*i.e.*, within seconds) lowered intracellular free Mg^{2+} [12-15]. Using these techniques coupled with ^{31}P -NMR spectroscopy and measurements of lumen sizes (and microvascular blood flows) in the intact brains of rodents, as well as use of a variety of isolated cerebral arteries, we found profound concentration-dependent vasoconstriction of the blood vessels and increasing ischemia, as evidenced by rising cellular concentrations of inorganic phosphate coupled to acidic intracellular pH, rises in deoxyhemoglobin, reduced mitochondrial levels of cytochrome oxidase and considerable loss of high-energy phosphate compounds [12-15].

Mg^{2+} is a co-factor for more than 500 enzymes, and is the second most abundant intracellular cation after potassium [35]. It is vital in numerous physiological, cellular and biochemical reactions including carbohydrate, lipid, protein, DNA and RNA metabolism, among other pathways [35,36]. Several epidemiologic studies in North America and Europe have shown that people consuming Western-type diets are low in Mg content (*i.e.*, 30-65% of the RDA for Mg) [37-40]; most such diets show that 60-80% of Americans are consuming 185-235 mg/day of Mg [39,40]. In 1900, in contrast, most Americans were consuming 450-550 mg/day of Mg [41]. Mg deficiency amongst the American and European populations could help to explain why, often, very low levels of alcohol can produce euphoric and hallucinatory events. This might also help to explain why many individuals do not experience euphoria or hallucinations after drinking more than two standard cocktail drinks containing alcohol, as their blood and tissue levels of Mg^{2+} are most likely elevated due to diets containing elevated levels of Mg.

But, does low Mg^{2+} -induced cerebral vasoconstriction and temporary ischemia in key areas of the brain account, in large measure for the euphoria, and if so, what is the molecular mechanism(s)? Approximately 40 years ago, two of us demonstrated using isolated cerebral, coronary, and peripheral arteries that a lowering of extracellular Mg^{2+} ($[Mg^{2+}]_0$) levels resulted in a rapid rise in intracellular free calcium ions just prior to contractile events [42-44]. More recently, our group found that lowering of $[Mg^{2+}]_0$ led to rapid activation of

several isoforms of protein kinase C, P-I-3 kinases, mitogen-activated kinases, tyrosine-activated kinases [45-51], and at least five major enzymes in the sphingolipid biosynthetic pathway [52-61]. Prior to these findings, we [41,52,62,63] and others [64,65] reported that a variety of sphingolipid bi-products, namely ceramides, sphingosine, sphingosine-phosphates, etc., can induce contraction of VSM cells in the brain and elsewhere in the body. We have reported that inhibition of the activation of the major synthetic pathways for ceramides in cerebral VSM cells, using specific inhibitors for each enzyme, resulted in marked attenuation of the contractions of cerebral blood vessels upon the lowering of $[Mg^{2+}]_0$ concomitant with reductions in the cellular rises of intracellular free Ca^{2+} [41,52,55-61, unpublished experiments]. Until very recently we believed that alcohol-induced cellular loss of $[Mg^{2+}]$ coupled to cellular entry and release of Ca^{2+} with rapid synthesis of ceramides might explain a great deal of alcohol-induced cerebral vasoconstriction and brain ischemic events. However, we now believe at least one more cellular compound, namely PAF and PAF-like molecules, probably plays an important role in alcohol-induced brain ischemic events, euphoria, and hallucinations.

Why focus on PAF? PAF and PAF-like molecules are known to affect multiple physiologic aspects of neuronal and cardiac functions [66-68]. For example, PAF can produce coronary arterial vasoconstriction, lower arterial blood pressure, increase coronary vascular resistance, release several lipid-like molecules from the heart, reduce cardiac output, decrease cardiac contractility, alter atrial and papillary muscle chronotropicity and membrane action potentials, as well as alter potassium currents in isolated cardiomyocytes [66-68]. All of these actions could lead one to believe that a rapid synthesis of PAF and PAF-like substances might play fundamental roles in alcohol-induced ischemia, euphoria, and hallucinations set into motion by a rapid lowering of $[Mg^{2+}]$. As a first step in testing this hypothesis, we determined whether a rapid reduction in $[Mg^{2+}]_0$ would result in the synthesis and release of PAF. Using isolated cerebral VSM cells in primary cell cultures, we recently reported that lowering $[Mg^{2+}]_0$ as predicted, does indeed rapidly lead to the cellular synthesis and release of PAF and PAF-like substances [69]. We and others have clearly demonstrated that PAF and PAF-like substances induce vasoconstriction of cerebral arterioles and venules in the intact brains of rodents using TV-image-intensification microscopy [69]. Whether or not use of inhibitors of PAF and ceramide synthesis coupled to increased dietary intake of Mg will attenuate the euphoric and hallucinatory actions of ethanol imbibed in cocktails, beers, etc., remains to be tested, but in our opinion seems like a worthwhile undertaking.

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