

Hypothesizing Darkness Induced Alcohol Intake Linked to Dopaminergic Regulation of Brain Function

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Received 23 January 2014; revised 22 February 2014; accepted 21 March 2014

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Abstract

Understanding the role of neurotransmission in the prefrontal cortex and mesolimbic brain regions has become the subject of intensive neuroscience research worldwide. In the 1970s, our group provided evidences that rats exposed to darkness significantly augmented their alcohol intake. At that time, we proposed that melatonin was the culprit. At around the same time, our laboratory, amongst a few others, proposed that dopamine-adducts with acetaldehyde to induce alcohol intake both in rodents and in humans. While the work in these areas has declined considerably over the years, more recent scientifically sound studies continue to show the importance of these earlier controversial ideas involving alcohol abuse and alcoholism. A review of the literature has provided impetus to systematically access the newer genetic and molecular neurobiological findings relevant to the physiological and psychological motives for high alcohol consumption in animals and humans alike. Thus, we hypothesize that darkness-induced alcohol intake is linked

not only to serotonergic-melatonin mechanisms, but also to dopaminergic regulation of brain mesolimbic pathways involving neuronal expression switching in response to long photoperiods affecting gene expression.

Keywords

Photoperiod; Alcohol Intake; Dopamine; Reward Pathway; Serotonin and Melatonin; Nocturnal

1. Introduction

In the mid 1960s, very little was known about brain function and neurotransmitter activity. At that time, even less was known about the interaction of neurochemicals and alcohol effects. In fact, one of the first relevant studies was executed by Myers and Veale in 1968, showing that preference for ethanol (alcohol) was significantly attenuated or totally eliminated in rats given p-chlorophenylalanine (PCA), a tryptophan hydroxylase inhibitor that selectively depletes brain serotonin content (Myers & Veale, 1968). The depleting action of PCA was more powerful than alpha-methyl-p-tyrosine, a tyrosine hydroxylase inhibitor that depletes brain catecholamines. This is not surprising considering anti-anxiety properties of alcohol in humans and in nonhuman animal models (Steiner, 1958). It is well-known that PCA induces “conflict” behavior in rats (Robichaud & Sledge, 1969), and this effect can be attenuated by the administration of 5-hydroxy-tryptophane (Geller & Blum, 1970). This suggests that PCA promotes anxiety and serotonin is an anti-anxiety brain substance.

It is well-known that levels of brain serotonin, especially in the pineal gland, are lowest during a dark phase, because of its conversion to melatonin via adenylate cyclase induced stimulation of N-Acetyltransferase activity which increase three-fold at night (Coon et al., 2012; Namboodiri, Sugden, Klein, Tamarkin, & Mefford, 1985; Raiewski, Elliott, Evans, Glickman, & Gorman, 2012). Specifically, pineal melatonin levels are low during the day, increase five to ten-fold at night, decrease during a light pulse at night, and rapidly increase to night levels following the light-dark transition (Namboodiri, Sugden, Klein, Tamarkin, & Mefford, 1985).

In the early 1970s, Blum’s group provided evidence for darkness-induced enhancement of ethanol drinking in rodents. The first report showed that rats placed in a dark closet drank more alcohol than those housed in the light (Geller, 1971). Blum theorized that the increased drinking was due to an increase in pineal melatonin, and subsequent experiments revealed this to be accurate, since injections of melatonin in rats exposed under “normal” photoperiods (nine hours of darkness during a 24-hour day) also displayed augmented ethanol intake (Geller, 1971; Sinclair, 1972).

Along these lines, a number of subsequent experiments revealed that enhanced ethanol consumption by not only rats, but also by Syrian hamsters indeed involved the pineal gland (Blum, Merritt, Reiter, & Wallace, 1973; Reiter, Blum, Wallace, & Merritt, 1973, 1974). Firstly, it was shown that a lesion to the superior cervical ganglion innervation to the pineal gland blocked darkness-induced ethanol drinking in Syrian hamsters (Reiter et al., 1974). Secondly, augmented ethanol drinking occurred in congenitally blind male rats never exposed to ethanol prior to experimental induction (Reiter et al., 1973). Finally, Blum et al. (1973) concluded that melatonin-induced drinking, due to a photoperiod, involved modifications in serotonin synthesis as a function of the photoperiod (Blum et al., 1973). While this was one theory concerning the neurochemical mechanism(s) of ethanol consumption, other earlier experiments suggested the role of condensation products, known as isoquinolines.

The most notable was the work of Davis and Walsh, who proposed that tetrahydropapaverline, a benzyltetrahydroisoquinoline alkaloid derivative of the biogenic amine, dopamine, and acetaldehyde, a product of alcohol, condenses and can induce ethanol intake in rodents (Davis & Walsh, 1970). Moreover, they suggested that alcohol and opiate addiction might have common neurochemical mechanisms. At the same time, others reported on biogenic amines (e.g., norepinephrine) (Cohen & Collins, 1970) and indolamines (serotonin) (Myers, 1989) aldehyde condensation products and their role in alcoholism. While these ideas met with great controversy, Blum’s group provided clear evidence that ethanol intake increased the metabolite of salsolinol in rat brain (Hamilton, Blum, & Hirst, 1978); salsolinol induced augmented alcohol intake; salsolinol acted like an opiate (Blum, DeLallo, Briggs, & Hamilton, 1982); and salsolinol induced alcohol withdrawal tremors (Blum, 1988; Blum, Hamilton, Meyer, Hirst, & Marshall, 1977).

In summary, abnormal intake of alcohol is related to opioid receptors in the brain, and this is based on early thinking. By comparison, the attenuation of alcohol drinking was associated with opioid receptor antagonists (Marshall, Hirst, & Blum, 1977), binding of a tetrahydroisoquinolin (THIQ) to opiate receptors in the brain (Blum, Eubanks, Wallace, Schwertner, & Morgan, 1976; Myers, 1989), and marked differences in enkephalin values in animals genetically predisposed to the ingestion of alcohol (Blum, Elston, DeLallo, Briggs, & Wallace, 1983). Finally, Myers (Myers, 1989) proposed that the dopaminergic reward pathways that traverse the mesolimbic-forebrain systems of the brain constitute an “integrative anatomical substrate for the adduct-opioid cascade of neuronal events which promote and sustain the aberrant drinking of alcohol”.

2. Relationship to Alcohol Use and Abuse

To our knowledge, other than work related to alcohol intoxication and withdrawal per se, little was known with regard to the role of dopaminergic function and vulnerability of aberrant ethanol consumption in humans (Blum, Eubanks, Wallace, & Schwertner, 1976). In fact, while dopaminergic mechanisms have been espoused for the role of dopamine and cocaine addiction (Dackis & Gold, 1985), a quick search in PUBMED revealed that the first real evidence for involvement of dopamine and alcoholism, especially genetic vulnerability, was provided by Blum et al. (Blum et al., 1990). Interestingly, the concepts related to dopamine adducts with alcohol lost favor in the scientific community in the mid 1980s until the early 2000s. However, there has been a new surge of studies that shows important pharmacological effects of at least salsolinol. To reiterate, ethanol excites dopamine neurons in the posterior ventral tegmental area (pVTA). This effect is responsible for ethanol’s motivational properties and may contribute to alcoholism.

Very recent studies by Melis et al. (Melis, Carboni, Caboni, & Acquas, 2013) demonstrated that salsolinol, when administered in pVTA, excites pVTA dopamine cells, elicits dopamine transmission in nucleus accumbens, and sustains its self-administration in pVTA. This finding is similar to morphine, indicating opioid like effects of salsolinol as noted earlier (Hamilton, Hirst, & Blum, 1979).

Review of the old and newer data clearly reveals that within the well-established brain reward circuitry, alcohol metabolites (e.g., dopamine and acetaldehyde) are involved in alcohol induced effects as indicted herein: 1) biologically active metabolites of alcohol can directly or indirectly increase the activity of VTA dopamine neurons, 2) alcohol and alcohol metabolites are reinforcing within the mesolimbic dopamine system, 3) inhibiting the alcohol metabolic pathway inhibits the biological consequences of alcohol exposure, 4) alcohol consumption can be reduced by inhibiting/attenuating the alcohol metabolic pathway in the mesolimbic dopamine system, 5) alcohol metabolites can alter neurochemical levels within the mesolimbic dopamine system, and 6) alcohol interacts with alcohol metabolites to enhance the actions of both compounds (Deehan, Hauser, Wilden, Truitt, & Rodd, 2013). Accordingly, there is a positive relationship between alcohol and alcohol metabolites in regulating the alcohol intake, and these biological consequences lead to an escalation to alcoholism (Deehan, Brodie, & Rodd, 2013). Furthermore, fortification of these results has adequately shown that salsolinol can induce dopamine release in the mesolimbic brain region, supporting earlier indications (Hipolito, Sanchez-Catalan, Granero, & Polache, 2009; Melchior, Simpson, & Myers, 1978). Finally, T-K Li’s group (Rodd et al., 2008) showed that infusions of salsolinol produced reinforcing effects in the pVTA of Wistar rats, and these actions were mediated by activation of DA neurons (D2/D3 receptors) and local 5-HT₃ receptors. There is also evidence that salsolinol’s reinforcing effects under stress involve endorphinergic mechanisms (Matsuzawa, Suzuki, & Misawa, 2000).

The importance of these findings involving alcohol metabolites underscores the potential role of reward circuitry signaling involving serotonergic, endorphinergic, gabaergic, and dopaminergic functionality in alcohol intake as well as reward deficiency syndrome (Blum, Gardner, Oscar-Berman, & Gold, 2012). We crafted this commentary relying on earlier studies suggesting that potential vulnerability to alcoholism may reside in not only the reinforcing properties of alcohol metabolites as indicated with salsolinol, but environmental alterations of light/dark cycles or photoperiods. Our understanding in the 1970s-1980s concerning alcohol vulnerability was very limited due to a paucity of gene related studies. In addition, during this earlier time period, little was known about the role of neurotransmitters in photoperiods. Thus, the impetus for this hypothesis is based in part on newer findings that will contribute to our knowledge on darkness-induced alcohol intake. Importantly, Yaegashi et al. investigated the relationship between salsolinol induced prolactin (PRL) release and photoperiod in goats. They found that the releasing effect of PRL by salsolinol was enhanced during long (dark) photoperiods. It suggests that this effect could be mediated by enhanced dopamine release (Yaegashi et al., 2012).

Since the 1970s, there has been a number of important articles on the brain reward cascade (Blum et al., 2000) that shed light on the interaction of serotonin, melatonin, enkephalins, acetylcholine, and dopamine on darkness-induced alcohol intake. Recently, Crespi (Crespi, 2012) further supported the role of melatonin in ethanol consumption in P (alcohol-preferring) rats by blocking spontaneous consumption of ethanol with a melatonin antagonist GR128107. It also has been shown that 10% chronic ethanol significantly reduces pineal peak melatonin synthesis by 70% partly, due to a phase delay in arylalkylamine N-acetyltransferase gene expression (Peres et al., 2011).

Ethanol preferring C57Bl/6J mice “drink in the dark” (DID) until intoxicated (model for binge drinking), and this effect involves nicotinic acetylcholine type brain receptors (nAChRs). It was found that nAChRs are indeed involved in ethanol intake in the DID paradigm. Specifically, the nicotinic acetylcholine receptor antagonist mecamylamine not only reduced ethanol consumption of these mice in the dark, it also blocked ethanol activation of dopaminergic neurons (Hendrickson, Zhao-Shea, & Tapper, 2009). This work is in agreement with earlier experiments by Ericson et al. showing that ethanol enhances accumbal dopamine levels via indirect activation of VTA nAChRs (Ericson, Molander, Lof, Engel, & Soderpalm, 2003). It is noteworthy that melatonin also regulates an endogenous opioid system (EOS)-circadian rhythm. The work by Miguel Asai et al. (2007) suggests that during the dark phase, melatonin enhances the EOS by increased tissue content of enkephalins in both hypothalamus and hippocampus of the rat brain, and in constant light the absence of melatonin leads to a decrease of tissue enkephalins (Miguel Asai et al., 2007). This may have some relevance in terms of understanding the role of enkephalins inhibitory effect on GABA neurons leading to altered dopamine release during photoperiods.

A very recent study by Dulcis et al. (2013) suggested that photoperiod-induced neurotransmitter switching could regulate brain function and subsequent adult behavior in rats (Dulcis, Jamshidi, Leutgeb, & Spitzer, 2013). They found that populations of interneurons in the adult rat hypothalamus switched between dopamine and somatostatin expression in response to exposure to short- and long-day photoperiods. Interestingly, changes in postsynaptic dopamine receptor expression matched changes in presynaptic dopamine, whereas somatostatin receptor expression remained constant. Moreover, pharmacological blockade or ablation of these dopaminergic neurons led to anxious and depressed behavior, “phenocopying” performance after exposure to the long-day photoperiod. Thus, during darkness, dopaminergic expression is reduced and this could be responsible in part for our previous findings involving darkness-induced ethanol intake (Blum et al., 1973; Reiter et al., 1973, 1974). This notion is fortified by their additional finding that exposure of the short-day photoperiod induced the synthesis of new dopaminergic neurons that “rescued” the resultant behaviors observed during the dark phase (Dulcis et al., 2013).

3. Conclusion

In summary, we are encouraged that following many years of research (Bruijnzeel & Gold, 2005; Dackis et al., 1984; Ebadi, Weiss, & Costa, 1970), the neurochemical mechanisms involved in the now established darkness-induced drinking paradigm has been further advanced (Sleipness, Jansen, Schenk, & Sorg, 2008). Based on the findings espoused in this hypothesis, the newer concepts of the role of both dopamine adducts (Hamilton, Blum, & Hirst, 1980; Sallstrom Baum, Hill, Kiianmaa, & Rommelspacher, 1999) and darkness-induced dopamine switching provides a fruitful avenue of investigation (El Halawani, Kang, Leclerc, Kosonsiriluk, & Chai-seha, 2009). While many future studies certainly will clarify the role of gene polymorphisms (Blum et al., 1990; Wang, Simen, Arias, Lu, & Zhang, 2013) including epigenetics and related behavioral endophenotypes, the concept that all roads lead to dopamine certainly continues to be an important therapeutic target ultimately leading to prevention of relapse and potential abolition of alcoholism (Balldin, Berggren, Berglund, & Fahlke, 2013; Blum, Fatterman, & Pascaro, 1977; Dahlgren et al., 2011; Self & Nestler, 1998).

Acknowledgements

We appreciate the expert edits of Margaret A. Madigan, as well as the PATH staff including Florian Kreuk, Mona Li, Kristina Dushhaj, and Courtney Trudesdell. The preparation and review of the manuscript was supported in part by funds from the National Institutes of Health, NIAAA (R01-AA07112 and K05-AA00219) and the Medical Research Service of the US Department of Veterans Affairs (Marlene Oscar-Berman). Dr. Kenneth Blum and Eric R. Braverman are the recipients of a grant from Life Extension Foundation, Ft. Lauderdale, Flor-

ida. Dr. Badgaiyan is supported by the National Institutes of Health grants 1R01NS073884 and 1R21MH073624, and VA Merit Review Awards CX000479 and CX000780.

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