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Review

Alcohol-related amnesia and dementia: Animal models have revealed the contributions of different etiological factors on neuropathology, neurochemical dysfunction and cognitive impairment

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ABSTRACT

Chronic alcoholism is associated with impaired cognitive functioning. Over 75% of autopsied chronic alcoholics have significant brain damage and over 50% of detoxified alcoholics display some degree of learning and memory impairment. However, the relative contributions of different etiological factors to the development of alcohol-related neuropathology and cognitive impairment are questioned. One reason for this quandary is that both alcohol toxicity and thiamine deficiency result in brain damage and cognitive problems. Two alcohol-related neurological disorders, alcohol-associated dementia and Wernicke-Korsakoff syndrome have been modeled in rodents. These pre-clinical models have elucidated the relative contributions of ethanol toxicity and thiamine deficiency to the development of dementia and amnesia. What is observed in these models—from repeated and chronic ethanol exposure to thiamine deficiency—is a progression of both neural and cognitive dysregulation. Repeated binge exposure to ethanol leads to changes in neural plasticity by reducing GABAergic inhibition and facilitating glutamatergic excitation, long-term chronic ethanol exposure results in hippocampal and cortical cell loss as well as reduced hippocampal neurotrophin protein content critical for neural survival, and thiamine deficiency results in gross pathological lesions in the diencephalon, reduced neurotrophic protein levels, and neurotransmitters levels in the hippocampus and cortex. Behaviorally, after recovery from repeated or chronic ethanol exposure there is impairment in working or episodic memory that can recover with prolonged abstinence. In contrast, after thiamine deficiency there is severe and persistent spatial memory impairments and increased perseverative behavior. The interaction between ethanol and thiamine deficiency does not produce more behavioral or neural pathology, with the exception of reduction of white matter, than long-term thiamine deficiency alone.

1. Introduction

Alcohol addiction is a severe disorder with many long-lasting health consequences—one of which can be impaired cognitive functioning. Numerous studies have reported that 50–75% of detoxified alcoholics have some type of cognitive or memory disturbance (for reviews, see Dufour (1993), Parsons and Nixon (1993), Smith and Atkinson (1995)). Furthermore, chronic alcohol consumption can lead to at least two long-lasting neurological disorders associated with severe cognitive dysfunction: alcohol-associated dementia (AAD) and Wernicke-Korsakoff syndrome (WKS). The neurotoxic effects of long-term heavy alcohol consumption are believed to produce AAD, whereas long-term heavy alcohol consumption in combination with dietary deficiencies—particularly thiamine—can lead to WKS. Although WKS is a nutrition deficiency disorder, it is most frequently reported in alcoholic patients (Kopelman, Thomson, Guerrini, & Marshall, 2009). Indeed, it has been estimated that greater than 10% of alcoholic patients have symptoms of either AAD or WKS (Harper & Kril, 1990; Parsons & Nixon, 1993).

To gain mechanistic insights to the consequences of ethanol neural toxicity and thiamine deficiency on learning and memory function, a number of animal models of alcohol-related disorders have been developed. Some models isolate the effects of long-term or repeated high levels of ethanol exposure whereas others assess the effects of thiamine deficiency. Other work has assessed the synergistic interactions between ethanol toxicity and thiamine deficiency. The amount of ethanol-induced neural and behavioral change seems to be dependent on length of ethanol exposure, volume of alcohol, and degree of withdrawal signs or number of binge bouts (Crews & Nixon, 2009). If animals are allowed to progress through a severe a bout of thiamine deficiency (Zhang et al., 1995), there are massive lesions in the anterior and midline thalamus as well as the mammillary bodies. Furthermore, recent evidence demonstrates that thiamine deficiency alters hippocampal- and frontal cortical-dependent behaviors and neurochemistry.

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2. Human neurological disorders associated with chronic alcohol consumption

Autopsy evaluations and *in vivo* neuroimaging of the brains of diagnosed human alcoholics has revealed that 78% of this population exhibits some degree of brain pathology (Goldstein & Shelly, 1980; Harper, 1998). The clinical presentation of brain damage in alcoholics is heterogeneous and results in a range of cognitive abnormalities. This is likely due to that a multitude of factors present in the alcoholic lifestyle (head injury, liver disease, malnourishment) that can cause brain damage. However, key factors that are important for brain damage in chronic alcoholics are: amount of consumption, length of drinking history, and malnourishment.

In fact, the diagnosis of AAD requires a careful clinical examination as this disorder includes a wide range of disrupted cognitive capacities that overlap with other types of dementia. Thus, a key diagnostic feature for this type of dementia is a history of alcohol abuse. The DSM-IV-TR (American Psychiatric Association., 2000) defines AAD as including memory impairment in addition to one or more other cognitive symptoms. The cognitive disturbances can include: aphasia (inability to use or understand language), apraxia (failure to make purposeful movements), agnosia (difficulty in identify objects), or disturbance in executive functioning (deficits in planning, organizing, attention, and/or changing cognitive strategies). In addition, the diagnosis of AAD cannot be made when a patient is acutely intoxicated or in the process of alcohol withdrawal.

A heavy drinking history is a cardinal feature in the criteria for AAD: Specifically, more than 35 drinks/week for men or 28 drinks/week for women for a period of 5 years. An additional component is the impairment of both executive control and memory that persists after 60 days of abstinence (Olsin et al., 1998; Schmidt et al., 2005). Alcoholic-associated dementia is estimated to make up about 10% of all dementia cases and heavy drinking history is a significant contributing factor to the development of other forms of dementia (Smith & Kiloh, 1981). Although the existence of AAD is widely acknowledged by health professionals, it is not often identified due to the diffuse criteria and overlapping symptomology common in other cognitive disorders (Gupta & Warner, 2008).

In contrast, the clinical diagnosis of WKS has distinct behavioral criteria. Wernicke's encephalopathy, which is the acute phase of WKS, is diagnosed by a classic triad of symptoms: oculomotor disturbances, motor-ataxia abnormalities, and global confusion (Victor, Adams, & Collins, 1971). The primary diagnostic feature of WKS is profound amnesia, both retrograde and anterograde (Victor, Adams, & Collins, 1989), but there are also impairments of perceptual and abstract problem solving skills (see Butters & Brandt, 1985; Parsons & Nixon, 1993). Despite these clear diagnostic criteria, WE and WKS is diagnosed more commonly in alcoholics at post-mortem than when while the patients are alive (Harper, 2007; Torvik, Lindboe, & Rogde, 1982). Indeed, post-mortem prevalence rates of WKS are 1–2% in the general population and 12–14% in the alcoholic population (Harper, 1998; Harper et al., 1985).

A number of reviews in the human literature (Bowden, 1990; Harper, 1998; Joyce, 1994; Victor et al., 1989) suggest that a clear clinical distinction between AAD and WKS may be unwarranted. This argument is based on the fact that it is difficult to determine the dietary status of many alcoholics making WKS an under-diagnosed disorder (Harper, 1998; Joyce, 1994). By this explanation, mild subclinical episodes of thiamine deficiency can account for most cases of AAD. Proteomic studies have shown that thiamine status is also altered in non-WKS alcoholics (Alexander-Kaufmann, Harper, & Wilce, 2007). This finding provides some evidence that mild-to-moderate thiamine deficiency plays a role in the neurodegeneration observed in chronic alcoholics.

The cognitive decline observed in AAD patients is more variable than that reported in WKS patients. Alcoholic-associated dementia is said to result in "global" cognitive decline across a wide range of skills involving perceptual motor, visual spatial, abstract problem solving, as well as learning and memory processes (see Oscar-Berman, Kirkley, Gansler, & Couture, 2004; Parsons & Nixon, 1993; Tartar, 1975). The key behavioral features of WKS are profound amnesia that impedes new episodic and declarative learning and recall as well as the appearance of confabulation (Kopelman et al., 2009). In the human patient there is much overlap between AAD and WKS in both neuropathology and behavioral symptoms (Bowden, 1990; Harper, 1998; Joyce, 1994). What is missing is a "gold standard" for the neurological (both brain and behavior) diagnosis of AAD as distinct entity from WKS. This quandary results in problems for the clinical diagnosis of both syndromes (Harper, 1998; Olsin et al., 1998. Others (Lishman, 1986; Lishman, 1990; Smith & Atkinson, 1995) argue that AAD and WKS are distinct disorders with overlapping clinical symptoms. This "dual vulnerability hypothesis" states that the development of these disorders in certain individuals likely involves numerous factors. One key factor that has been hypothesized is a genetic pre-disposition for the development of WKS (alterations in thiamine metabolism) or AAD (susceptibility to alcohol neurotoxicity). However, in human patients it is difficult to distinguish primary alcohol-induced pathology from brain damage due to the alcoholic lifestyle (vitamin deficiency, malnutrition, head trauma, liver disease, diabetes). Accordingly, neuropathological data as subsequently described in this review lends further support towards a continuum on the effects of alcohol to thiamine deficiency on the brain and memory.

2.1. Neuropathology in alcohol-related disorders

The earliest reports of brain abnormalities in those with excessive alcohol consumption were non-specific findings from CT imaging and post-mortem data. For instance, CT studies in alcoholics described reductions in brain volume (Harper & Blumbergs, 1982) and clinical pathology reports revealed reduced brain weights in alcoholics compared to controls (Harding, Halliday, Ng, Harper, & Kril, 1996). The most commonly reported findings in the brains of alcoholics are sulcal widening and ventricular enlargement as well as cortical white matter shrinkage, hippocampal abnormalities, and cell loss in the septal region and cerebellum (Harper, 1998; Lishman, 1990; Parsons & Nixon, 1993; Pfefferbaum et al., 1992).

It has been well documented that there is neuronal loss in specific regions of the cerebral cortex, hypothalamus, and cerebellum of the alcoholic brain (Harper, Kril, & Daly, 1987). However, a stereology study in humans (Harding, Wong, Svoboda, Kril, & Halliday, 1997) found that there was no hippocampal neuronal loss in alcoholics compared to non-alcoholics. It was discovered that the hippocampal volume decrease observed in human alcoholics occurs from white matter loss and not from gray matter. Furthermore, both pathological (Harper & Kril, 1990) and imaging studies (Pfefferbaum, Lim, Desmond, & Sullivan, 1996) demonstrated reduced corpus callosum volume and white matter degeneration in the cerebellum of alcoholics (Sullivan, Deshmukh, & Desmond, 1998). The mechanism for white matter loss appears to be the occurrence of both myelin loss and the degradation of axonal circuitry (Pfefferbaum & Sullivan, 2005).

The frontal lobes appear to be more vulnerable to alcohol-related brain damage than other cerebral regions (Dirksen, Howard, Cronin-Golomb, & Oscar-Berman, 2006; Oscar-Berman et al.,