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The Neuropathology of Alcohol-specific Brain Damage, or Does Alcohol Damage the Brain?

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Abstract. The aim of this review is to identify neuropathological changes that are directly related to the long-term use of excessive amounts of alcohol (ethanol). There is still debate as to whether alcohol per se causes brain damage. The main problem has been to identify those lesions caused by alcohol itself and those caused by other common alcohol-related factors, principally thiamin deficiency. Careful selection and classification of alcoholic cases into those with and without these complications, together with detailed quantitative neuropathological analyses, has provided us with useful data. There is brain shrinkage in uncomplicated alcoholics which can largely be accounted for by loss of white matter. Some of this damage appears to be reversible. However, alcohol-related neuronal loss has been documented in specific regions of the cerebral cortex (superior frontal association cortex), hypothalamus (supraoptic and paraventricular nuclei), and cerebellum. The data is conflicting for several regions: the hippocampus, amygdala and locus ceruleus. No change is found in the basal ganglia, nucleus basalis, or serotonergic raphe nuclei. Many of the regions that are normal in uncomplicated alcoholics are damaged in those with the Wernicke-Korsakoff syndrome. Dendritic and synaptic changes have been documented in uncomplicated alcoholics and these, together with receptor and transmitter changes, may explain functional changes and cognitive deficits that precede the more severe structural neuronal changes. The pattern of damage appears to be somewhat different and species-specific in animal models of alcohol toxicity. Pathological changes that have been found to correlate with alcohol intake include white matter loss and neuronal loss in the hypothalamus and cerebellum.

Key Words: Alcohol; Brain damage; Ethanol; Neuropathology; Neuronal loss; Thiamin deficiency; White matter.

INTRODUCTION

There is little doubt that excessive consumption of alcohol over a considerable period of time may lead to an impairment of cognitive function. Specific alcohol-related disorders such as the Wernicke-Korsakoff syndrome (WKS), hepatic encephalopathy, and pellagra cause clinical dementia syndromes, but when these have been excluded there are still a number of alcoholics who have cognitive deficits. However, there are major problems in the clinical classification of alcoholic cases, particularly with regard to the diagnosis of WKS. Retrospective analyses of cases of WKS that are diagnosed pathologically have shown that only about 20% of cases are diagnosed clinically, even after repeated hospital admissions of many of the cases (1, 2). Caine and her colleagues (3) have addressed this problem and have suggested operational criteria for the clinical classification of these cases. The new criteria for Wernicke's encephalopathy (WE) require 2 of the following 4 signs; (a) dietary deficiencies, (b) oculomotor abnormalities, (c) cerebellar dysfunction, and (d) either an altered mental state or mild memory impairment. An important observation was the coincidence of hepatic encephalopathy and WE in some alcoholics. We were unable to identify a subset of alcoholic patients with a dementia-like process when degenerative neuropathology and head injury had been excluded. Those cases who do not have any of the alcohol-associated disorders discussed above but who exhibit cognitive deficits have been labeled Dementia Associated with Alcoholism 291.20 in DSMIIIR (4). However, there is still some controversy as to whether such a condition exists. Victor and Adams (5) reviewed the clinical, neuropsychological, neuropathological, and neuroradiological evidence concerning alcohol-specific neurotoxicity and concluded that there was no need to invoke a separate entity due to the toxic effect of alcohol on the brain, as they could practically always account for the clinical state of their patients by one or a combination of the Wernicke-Korsakoff syndrome, acute and chronic hepatic encephalopathy, communicating hydrocephalus, Alzheimer disease, Marchiafava Bignami disease, ischemic infarction or anoxic encephalopathy. They emphasized that no one had established the pathologic basis for such a syndrome, but suggested that morphometric and other quantitative techniques might disclose abnormalities. Since that time many other receptor and neurotransmitter changes have been described in human and animal studies of alcohol toxicity, and these may cause cognitive dysfunction in the absence of structural abnormalities (6, 7). It must be emphasized that not all alcoholics have impairment of cerebral function. Butters and his colleagues (8) have shown that 30–50% of alcoholics will perform a range of neuropsychological tests within the normal range for controls. Moreover, in a recent study of Australian veterans from World War II, persistent lifelong consumption of alcohol and the level of intake did not seem to have any impact on cognitive performance or cause brain atrophy (on CT scans), even in those drinking at "hazardous" (40–60 g per day) or "harmful" (<60 g per day) levels (9). However, Tuck and Jackson (10) reported that

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people who drink excessively (median daily intake of 180 grams per day) and are not overtly demented frequently reveal frontal lobe dysfunction that may be relatively subtle. Thus, there seems to be a wide spectrum of the effects of alcohol on the brain with considerable individual variability in susceptibility. The aim of this review is to evaluate the neuropathological data with regard to changes in the brain that are caused by alcohol per se in order to assess its true neurotoxicity and better understand regional selectivity, mechanisms of toxicity, and interrelationships with other pathogenetic factors.

REGIONAL NEUROPATHOLOGY OF ALCOHOL NEUROTOXICITY

The existence of specific neurotoxic effects of alcohol on the central nervous system (primary alcoholic dementia or dementia associated with alcohol) can be approached from a number of viewpoints. As discussed above, clinical and neuropsychological data point towards such an entity. Moreover, as neuroimaging techniques have become more sophisticated, abnormalities at the structural and functional level are being identified in uncomplicated alcoholics who are cognitively impaired (11, 12) Nevertheless, the ultimate proof of the existence of this entity rests with the identification of the pathological substrate of alcohol-specific neurotoxicity.

Data from human neuropathologic studies is limited because of difficulties in obtaining material suitable for such studies. Ideally, cases should have been tested clinically and neuropsychologically before death and cognitive deficits documented. Other causes of cognitive dysfunction such as Alzheimer disease, strokes, WKS, and hepatic encephalopathy must be excluded clinically, and more importantly, pathologically, in order to address the question of alcohol-specific neurotoxicity. That is, all cases used for study must be "uncomplicated" alcoholics with no other neurological diseases, including those nutritional and metabolic disorders that are so commonly associated with alcoholism. In fact, there is some evidence to suggest that alcoholics may suffer from episodes of subclinical thiamin deficiency that will not manifest clinically as classical WKS (13, 14), making the selection of cases even more difficult. This would explain why about eighty percent of cases diagnosed pathologically as WKS are not recognized as clinical WKS, even after repeated admissions to major teaching hospitals (1, 2). Even in the controlled situation of a rat model, a single episode of mild thiamin deficiency appears to selectively damage cortical white matter tracts in the absence of typical WE pathology (15). Thus, unless we can find a more specific pathological marker for thiamin deficiency, it is difficult to exclude thiamin deficiency as a cause of the pathological changes in the brains of alcoholics. Nevertheless, the following is a review of the neuropathological data derived largely from cases which have been very carefully screened by collecting information from local doctors and families of the deceased and have been studied in great detail pathologically to exclude other complicating conditions.

BRAIN "SHRINKAGE"

Brain weight studies show that a group of uncomplicated alcoholics (drinking more than 80 grams of alcohol per day for more than 15 years) had a significantly reduced brain weight (mean of 1352 g) compared with controls (mean of 1433 g) (16). The loss of brain tissue can be more accurately defined by expressing the brain volume as a proportion of intracranial volume. This ratio has been termed the pericerebral space (PICS) (17), and in a group drinking from 30–80 grams of alcohol per day, the PICS is 11.3% compared with 8.3% in controls (18). In a study by Harding and colleagues (19), a correlation between the degree of brain atrophy and the rate and amount of alcohol consumed over a lifetime was shown.

WHITE MATTER CHANGES

The reduction in brain weight and volume is largely accounted for by a reduction in the white matter volume of the cerebral hemispheres rather than a loss of cortical tissue (20, 21). A study by de la Monte (21) showed an absolute increase in the size of the ventricles that was roughly equal to the amount of white matter lost. There was a significant age effect in both control and alcoholic groups that appeared to be parallel (22); this raised the issue of whether or not there is a relationship between aging and alcohol (23). A study by Kril and colleagues (24) showed reduced volumes of white matter in alcoholics with WKS, and two important observations were made in these cases—the prefrontal white matter was the most markedly reduced and there was a negative correlation between the white matter loss and the maximum daily alcohol consumption. An experimental study in dogs has also shown that the white matter is more vulnerable than the gray matter (25). MRI studies have confirmed that there is cerebral white matter loss in alcoholics (12), and have also shown that there is a component of the loss that is reversible given a significant period of abstinence (26, 27). Imaging studies have also shown that the frontal lobes are more shrunken than other brain regions (28). There is a greater proportion of white matter compared with cortical gray matter in frontal regions that may explain this finding. The ratio of gray matter to white matter is 1.22 in the frontal region and 1.40 in occipital lobes (22). The white matter of the cerebellar vermis is also reduced in volume in alcoholics when compared with controls (29). Sullivan and her colleagues have shown that a subset of alcoholics, those with a history of withdrawal seizures, have reduced white matter volumes in the temporal lobe (30). These authors were unable to correlate this white matter loss with alcohol

dose. The question of alcohol withdrawal and brain damage is discussed further in the section dealing with the hippocampus. The corpus callosum is significantly reduced in thickness in alcoholics (3.19 ± 0.66 mm) when compared with age and sex-matched controls (4.02 ± 0.66 mm). In this study, a number of the alcoholics had WKS (31). The corpus callosum can be well visualized and measured using MRI scans (32), and has been shown to be thinned in older alcoholic men (33). Thus, corpus callosal thickness could be measured in vivo to assess brain shrinkage and to identify and quantitate the reversibility of the brain shrinkage that has been documented with abstinence (26). Microscopically, there are no obvious lesions in the white matter of the cerebral hemispheres of uncomplicated alcoholic subjects, although an almost total loss of myelinated fibers has been demonstrated in the mammillary bodies of WKS cases (34). Alling and Bostrom (35) showed similar changes in 9 chronic alcoholic subjects without WKS and further analyzed the mammillary body tissue chemically. They found significantly lower concentrations of phospholipids, cholesterol, and cerebroside, implying a loss of myelin in the alcoholic cases. However, studies of the lipid profiles of the white matter in different alcoholic groups have shown only minor alterations (36). Even when high-performance liquid chromatographic methods are employed in the analysis of lipid class composition in controls and alcoholics, no significant differences were found (37). The subtle nature of the white matter changes in the cerebral hemispheres are borne out by other physical and chemical studies of the white matter. The specific gravity of the frontal, parietal and occipital white matter in alcoholics and age- and sex-matched controls show no significant differences (38). It has been suggested that reversible white matter shrinkage seen in alcoholics is caused by changes in hydration, but neurochemical (39) and imaging studies (40) refute this hypothesis. In a 5-week follow-up of abstinent alcoholics, Mann and his colleagues (41) reported a significant drop in CSF volume, but no increase in T2 times, which would have been predicted if brain tissue rehydration underlay the process. Wiggins and his colleagues (42) showed a slight increase in the water content of the white matter with aging. The water gain from 30 to 90 years amounts to 50 mg/g brain. This was associated with a decrease in total protein and specifically a decrease in the myelin and myelin-like fractions. The loss of myelin membrane amounted to 43 mg/g brain. They included alcoholics in their study and showed that heavy alcohol consumption was associated with an increase in total protein in the white matter and the age-related loss of myelin was accelerated (42). Ultrastructural studies of the effects of alcohol on the structure of CNS myelin in an experimental model during development have been carried out by Phillips, who has shown a reduction in the relative thickness of myelin sheaths in rat optic nerve. The myelin sheaths have fewer lamellae than equivalent control material (43). Such changes could cause significant neurological dysfunction.

An important observation, made by a number of neuroradiology groups, is that brain shrinkage is reversible in a proportion of alcoholics given a prolonged period of abstinence (27, 40, 44) The implication is that there is a potentially reversible structural change in the white matter in alcoholics. Thus, there may be two different abnormalities of the white matter. One is almost certainly a permanent loss of white matter related to axonal degeneration subsequent to neuronal loss in cortical and/or subcortical regions as discussed below. The second component may be a subtle structural change, perhaps in the myelin, which accounts for the reversible white matter change. Lancaster has addressed this issue and suggested several mechanisms which might play a role (45).

CEREBRAL CORTEX

There is an apparent atrophy of the cerebral cortex with widening of the cortical sulci and narrowing of the gyri in many alcoholic patients. This could be explained by loss of white matter, as discussed above. However, a number of pathological (21) and radiological studies (28) have suggested that there is a slight reduction in the volume of the cerebral cortex. The recent study by Kril et al showed that there were only cortical volume changes in those alcoholic patients with WKS. In this study, Kril et al identified changes in the frontal association cortex, medial temporal lobe (including amygdala), and the hippocampus (24). At the microscopic level, the first quantitative study documenting neuronal loss in alcoholics was published in 1987 by Harper et al (46). There was a 22% reduction in the number of neurons in the superior frontal cortex (Brodmanns area 8), but no significant change in the primary motor (area 4), frontal cingulate (area 32) or inferior temporal (areas 20 and 36) cortices (47). However, those studies included cases with WKS and cirrhosis, and the counting techniques were less reliable than those in use today. Badsberg-Jensen and Pakkenberg (48) used unbiased sampling and the optical dissector technique to estimate the total number of neurons in the neocortex in 11 alcoholic and control patients. They found no difference in the 2 groups, although it should be noted that selective neuronal loss from particular cytoarchitectural regions could be missed using this technique. Recently, Kril et al calculated regional volumes and unbiased estimates of neuronal numbers in a number of cortical regions. They showed, in a small group of uncomplicated alcoholics, that there was a selective loss of neurons from the superior frontal association cortex (23%), but no loss from the motor cortex (24). There are clinical and radiological data that support the finding of selective frontal lobe damage in alcoholics (28, 49). An analysis of the pattern of neuronal loss from

the superior frontal cortex in alcoholics revealed that large pyramidal neurons, with a somal area greater than 90 μm, were selectively lost (50). This population of large neurons has been recognized as being more vulnerable in both Alzheimer disease (51) and in the normal aging process (52). There is no evidence to suggest that particular layers of the cerebral cortex are more vulnerable than others (50). It appears that the neuronal loss involves non-GABAergic pyramidal neurons, as numbers of calbindin, calretinin, and parvalbumin-immunoreactive neurons are unaltered (24). Changes have been documented at the dendritic and synaptic levels in both human material and in experimental models of alcohol toxicity. Harper and Corbett have shown a significant reduction in the dendritic arbor of layer III pyramidal neurons in both the superior frontal and motor cortices of alcoholics (53). Ferrer et al (54) showed a decrease in the density of dendritic spines in layer V cortical pyramidal neurons in uncomplicated alcoholics. Similar findings have been documented in animal models of alcohol toxicity (55). McMullen et al (56) made an important observation in this area when they showed that 5 months of exposure to alcohol in rats caused a significant reduction in the branching of the dendritic arbor of hippocampal neurons, but that the arbor returned towards normality after 2 months of abstinence.

HIPPOCAMPUS AND AMYGDALA

The hippocampal formation has been relatively poorly studied in alcoholic subjects despite the fact that pathological changes in the hippocampus have dominated the literature on experimental models of alcohol toxicity as discussed herein. A number of these models have shown that neurons in the hippocampus are selectively damaged by alcohol (56, 57). Using MRI image analysis, Sullivan and her colleagues (58) showed a 4–6% reduction in the volume of the hippocampus in alcoholics. The change was greatest in the anterior segment, but there was no correlation between alcohol consumption or impaired memory function and the degree of atrophy. Those alcoholics with a history of withdrawal seizures had significantly smaller temporal lobe white matter volumes (30). There have been 2 quantitative pathological studies of the hippocampus in alcoholics (24, 59). Bengochea and Gonzalo showed that there is an age-related reduction in the density of neurons in alcoholics, whereas Kril et al, in a carefully conducted study, showed no cell loss (24). However, the latter group did note a trend toward a reduction in the volume of the hippocampus in the uncomplicated alcoholics and in those with WKS, but this change could also be explained by loss of white matter. In spite of the apparent lack of structural changes to hippocampal neurons in alcoholics, recent studies have shown that hippocampal-dependent learning is impaired by alcohol in a dose-dependent fashion (60).

Two quantitative studies of the amygdala are reported in the literature. Kril et al (24) noted a significant reduction in the volume of the amygdala complex only in those alcoholics with WKS, whereas Alaverez et al found a significant reduction in neuronal density in alcoholics of all ages (61). In addition, the latter group showed that rats treated with alcohol also had reduced neuronal densities in the amygdala.

Epilepsy is a relatively common clinical syndrome in alcoholics. Wilkinson et al (62) found an incidence of 7.8% in their study of 1,000 alcoholics, and many of these cases will have hippocampal sclerosis. In a recent study of the prevalence of the WKS in forensic autopsies, 25 cases were identified out of 2,212 autopsies, a prevalence of 1.1% (63). There were 130 cases with a history of alcohol-related problems, and 12 (9.2%) had sclerosis of the hippocampus.

THALAMUS

There is a considerable literature on thalamic pathology in alcoholics, but the majority refers to those patients with associated thiamin deficiency (WKS) (34, 64). There is relatively little information on uncomplicated alcoholics. The most important piece of data linking alcohol per se with thalamic disease is the recent finding of a significant correlation between thalamic volume and maximum daily alcohol consumption (24). Although there are no obvious specific macroscopic or microscopic abnormalities in the thalamic nuclei in uncomplicated alcoholic cases, significant changes in total neuronal counts, neuronal density, and mean neuronal size can easily be overlooked unless detailed quantitative analyses are carried out. An experimental study of the effects of alcohol on thalamic nuclei was published by Berachochea et al (65). They showed that there was a significant decrease in the volumes of the medial dorsal and anterior nuclei of the thalamus in mice who had consumed alcohol for 6 to 7 months. Data on neuronal counts in the anterior and medial dorsal nuclei of the thalamus in different alcoholic groups is currently in progress by our group. Preliminary studies suggest that there is no change in uncomplicated alcoholic cases, but a difference in the pattern of pathology has been noted in cases of Wernicke's encephalopathy when compared with cases of Korsakoff's psychosis. It appears that the amnestic state in the latter group relates to severe neuronal loss in both the anterior and medial dorsal thalamic nuclei (66).

HYPOTHALAMUS

Pathologic changes in the hypothalamus are also well described in alcoholics with WKS—lesions are seen in the mammillary bodies in almost 100% of cases (14). However, Harding et al have now shown that both the supraoptic and paraventricular nuclei are also affected in

alcoholic groups (19). We analyzed arginine vasopressin-immunoreactive neurons in the magnocellular hypothalamic nuclei of 10 alcoholic cases (5 uncomplicated alcoholics and 5 with WKS). The volumes of the supraoptic and paraventricular nuclei correlated significantly with the total number of neurons and with the number of vasopressin-immunoreactive neurons. These measures also correlated with the maximum daily intake of alcohol, which was assessed carefully, although retrospectively. There was loss of neurons at consumption levels greater than 100 grams of ethanol per day. The principal effect was on the supraoptic nucleus, although neuronal loss was also noted in the paraventricular nucleus in cases with long histories of alcohol consumption. These changes could result in fluid imbalances and inappropriate responses to osmotic stresses, which are common in alcoholics. While there do not appear to be any other similar studies in humans, the chronic consumption of alcohol in rats significantly reduces the number of vasopressin-producing neurons in the supraoptic nucleus (67).

BASAL GANGLIA

The basal ganglia have also received little attention in studies on alcohol-related brain damage. Harper and colleagues (22), in their analysis of brain shrinkage in alcoholics, measured the volume of the "basal ganglia" (which included the thalamus and hypothalamus) and found no significant loss of tissue from this region. However, it should be noted that the point counting technique used in this study was not sensitive enough to detect subtle changes in the volume of a structure, which constitutes only about 5% of the total hemisphere volume. Kril et al (24) used a more sensitive method of volume estimation and were unable to show any change in the volumes of the caudate, putamen, or globus pallidus in any of their alcoholic groups. Microscopic damage to the basal ganglia is not apparent in alcoholics, although no comprehensive quantitative studies have been published. Victor and colleagues (34) did not even comment on the involvement of the basal ganglia in their extensive examination of patients with the WKS. Studies in animal models of alcohol toxicity have identified abnormalities in neurotransmitter receptor binding in the basal ganglia. Freund and his colleagues found a loss of muscarinic cholinergic receptors from the putamen in alcoholics, but found no change in the benzodiazepine receptors (68).

NUCLEUS BASALIS

Some authors have suggested that the amnestic disorder of Korsakoff's psychosis relates to damage of the cholinergic magnocellular neurons in the nucleus basalis in the basal forebrain. However, most of the early studies used flawed quantitative techniques and few groups addressed the question of the effects of alcohol per se. Arendt et al (69) compared the pathological changes in the nucleus basalis in Alzheimer disease, Parkinson disease, and Korsakoff's psychosis. There was a significant loss of neurons in Alzheimer disease (30%), Parkinson disease (23%), and Korsakoff's psychosis (53%). However, they also studied 5 uncomplicated alcoholics, and the mean neuronal counts were no different from control data. Cullen and her colleagues (70) have quantitated magnocellular neurons in the nucleus basalis (CH4) of uncomplicated alcoholics and those with Wernicke's encephalopathy and Korsakoff's psychosis. There was no significant difference between controls and uncomplicated alcoholic cases and there was no correlation between neuronal numbers and lifetime alcohol consumption. As previously reported, CH4 cell numbers in control and alcoholic groups correlated with age. There was a significant reduction in numbers of neurons in the Wernicke's encephalopathy group and those with Korsakoff's psychosis (24% and 21%, respectively). Although there was no causal relationship between the neuronal loss and the amnesia, there appeared to be a relationship with the attention deficits seen in some of the cases. It is of interest to note that neurofibrillary tangles have been reported to be common in the magnocellular neurons of the nucleus basalis in alcoholics with WKS (71). These were seen using both silver impregnation techniques and tau immunohistochemistry (abnormally phosphorylated form). The number of tangles seen is considerably less than the number found in the average case of Alzheimer disease. There were only occasional tangles in the two uncomplicated alcoholic cases that were examined and there were no tangles or neuritic plaques in the cortex of any of the cases (including WKS cases). In all of the WKS cases and in some of the uncomplicated alcoholics, neurons in the nucleus basalis showed increased peroxidase activity. Neighboring astrocytes also showed an increase in peroxidase activity. The authors speculated that neurodegeneration of the nucleus basalis in chronic alcoholics, especially those with additional thiamin deficiency, begins with the formation of neurofibrillary tangles that may be linked to the presence of increased peroxidase.

LOCUS CERULEUS

Lesions in the noradrenergic locus ceruleus are said to cause impairment of attention and information processing, and there may be links with learning and memory. McEntee and Mair (72) used biochemical studies to address the question of abnormalities of noradrenergic pathways in alcohol-related brain damage. They have shown significant reductions of noradrenaline and its metabolites in the cerebrospinal fluid of WKS cases. Moreover, there is evidence of memory improvement with noradrenaline replacement therapy (72). There is still some controversy as to whether or not uncomplicated alcoholics have reduced numbers of noradrenergic neurons in the locus ceruleus. Arango et al found a 23% reduction of pigmented

neurons in the locus ceruleus in 5 alcoholic cases and suggested that this may contribute to their memory loss and depression (73). On the other hand, our research group has shown that there is no significant loss of neurons in the locus ceruleus in alcoholics, including those with WKS (74, 75). Halliday and Baker have written a critical analysis of these 3 papers and have shown that the age range of the control and alcoholic cases may account for the discrepant results (76). Analysis of the data from all of the studies using similar methods revealed that the number of locus ceruleus neurons in younger alcoholics (mean SD = 36,800 ± 6,900) was similar to the number in older alcoholics (36,400 ± 7,800) and older controls (35,600 ± 6,200) (76).

BRAINSTEM RAPHE NUCLEI

The median and dorsal raphe nucleus provide the primary source of serotonergic axons innervating large regions of the forebrain, particularly the cerebral cortex, the limbic system, and the hypothalamus. However, not all neurons in the median and dorsal raphe nuclei are serotonergic (43% and 35% of all neurons, respectively) (77). There has been considerable recent interest in the effects of alcohol on the serotonergic system as a result of the documentation of a number of biochemical and receptor abnormalities (78). Alcohol is said to have a biphasic effect on brain levels of serotonin (5HT); there is a transient initial release of 5HT from axon terminals followed by a long-lasting and marked depression of 5HT levels. Ballenger et al found significantly reduced levels of 5-hydroxyindoleacetic acid, a metabolite of 5HT, in the cerebrospinal fluid of 37 hospitalized alcoholics (79). Moreover, it has been found that the administration of serotoninergic receptor antagonists (5HT uptake inhibitors such as fluoxetine) significantly reduces alcohol consumption (80). Anatomical changes have been documented in the serotonergic system in rats who prefer alcohol (P rats), when compared with rats that do not prefer alcohol (NP) (81). Our group (77) has carried out quantitative morphometric studies of both the dorsal and median raphe nuclei in uncomplicated alcoholics and those with WKS. We used immunohistochemistry to identify the serotonergic neurons (PH8 antibody). Neuronal counts on spaced serial sections of the dorsal raphe nucleus area showed an estimated average total of 106,100 ± 19,500 (n = 8) serotonergic neurons in the uncomplicated alcoholics and 108,300 ± 11,800 (n = 8) in the controls (82). Although there was no significant difference between the 2 groups, and neuronal morphology and average size was similar, there was a reduction in the staining intensity of the reaction product in the dorsal raphe nucleus neurons of the alcoholic cases. In those alcoholic cases with WKS, there was a significant reduction in the number of serotonergic neurons (38,450 ± 13,430, n = 5). The loss varied at different levels throughout the rostro-caudal axis, but was particularly severe in the pons (83).

In the median raphe nucleus there was no significant difference between controls and uncomplicated alcoholics. There was an estimated average total of 59,560 ± 8,010 (n = 8) serotonergic neurons in the alcoholics, and 63,010 ± 8,900 (n = 8) in the controls (84). This is in contrast to the changes documented in alcoholics with WKS who had a 70% reduction in numbers of serotonergic neurons in the median raphe nuclei. The morphology of the neurons was the same in the control and uncomplicated alcoholic cases, but there was a reduction in the staining intensity of the reaction product in the alcoholic cases. This did not relate to other variables such as postmortem delay or the length of time in primary antibody. Thus, it appears that the serotonergic system is disrupted in alcoholics with WKS, but is structurally intact in uncomplicated alcoholics. This implies that the effects of alcohol on the serotonergic system, which have been documented in biochemical studies of alcoholic cases, are functional rather than structural.

CEREBELLUM

Atrophy of the cerebellum is commonly associated with alcoholism. Torvik and colleagues (85) reported that 26.8% of alcoholics and 38.6% of alcoholics with WKS had cerebellar atrophy. Both Harper (14) and Victor et al (86) studied patients with the WKS and found an incidence of cerebellar atrophy of 32% and 36%, respectively. Cerebellar atrophy has also be noted and quantitated in alcoholics using CT and MRI (87). Macroscopically, there is shrinkage of the folia, particularly the anterior superior cerebellar vermis. Preliminary data from our quantitative studies of the cerebellum from 7 controls, 4 uncomplicated alcoholics, and 6 alcoholics with WKS (using 50 m serial frozen sections) show a reduction in the volume of the white matter in the vermis, intermediate, and lateral zones (88). This correlates with our previous studies which highlighted a reduction in the volume of the molecular and medullary layers in the vermis (29). Microscopically, in the uncomplicated alcoholic cases, there is a decreased Purkinje cell density that has a spinocerebellar distribution. The neuronal loss correlated negatively with the amount of alcohol consumed per day (88). In alcoholics with the WKS, there was a 40% loss of Purkinje cells in the flocculus (vestibulocerebellum). There are many other analyses of neuronal counts and densities in the cerebellum of alcoholic cases. Phillips et al compared 16 controls with 13 uncomplicated alcoholics and 6 alcoholics with WKS. We found a 17% reduction in the number of Purkinje cells in the WKS cases and a 10% (not statically significant) reduction in the uncomplicated alcoholics (89). Studies of the dendritic arborization of Purkinje cells using Golgi impregnation techniques have revealed reduced arbor in alcoholics (3

of the 4 cases had WKS) (90) and in rats fed a diet containing alcohol (91). Pentney has reviewed the experimental data on the effects of long-term ethanol consumption on the cerebellum and has shown that the changes are more complicated than initially thought; i.e. alcohol can cause a nonrandom elongation of terminal dendritic segments (92). This is presumed to represent selective compensatory growth. There are suggestions in the literature that there are similarities between the morphological changes seen in aging and in the effects of alcohol. This question has been specifically addressed in a rat model, and Pentney has concluded that the dendritic changes are quite different (93).

Thiamin deficiency has been implicated in the etiology of alcohol-related cerebellar degeneration. Adams (94) described a disease identical to alcoholic cerebellar degeneration in malnourished individuals without alcoholism. Additional evidence pointing towards the importance of thiamin deficiency as the principal pathogenetic factor in alcoholic cerebellar degeneration is that the clinical features of the disorder have been shown to be reversed by the administration of thiamin, even in the presence of continued alcohol consumption (34). Thus, it seems that alcohol and thiamin deficiency can affect the cerebellum both structurally and functionally, and, although there is gathering evidence that the patterns of involvement are different, they may well be synergistic.

EXPERIMENTAL MODELS OF ALCOHOL NEUROTOXICITY

Experimental models of the effects of "chronic" exposure of the brain to alcohol have been developed by a number of groups. The distribution and extent of neuronal loss seems to depend on the duration of alcohol exposure, the magnitude and mode of exposure (ingestion, inhalation, etc), the genetic susceptibility of the species, and the strain of animals studied. As in the human studies, there is evidence pointing towards selective vulnerability of specific anatomical regions. Unfortunately, most studies have focused on single regions of the brain rather than using a single model and studying it comprehensively. In view of this, and the variability of the models used, it is difficult to gain a clear overview of the regional specificity and selectivity of alcohol-related brain damage in animals. Walker and his colleagues have reviewed the effects of chronic alcohol exposure on the hippocampus (95). The available evidence suggests that hippocampal pyramidal neurons, dentate gyrus granule cells, and local circuit interneurons in the hippocampus and dentate gyrus are all susceptible. CA1 region appears to be particularly sensitive to the neurotoxic effects. It has been suggested that alcohol withdrawal may play a role in brain damage, evidenced by the fact that a number of workers have shown that loss of granule cells in the dentate gyrus continues even after alcohol exposure stops (96). Hoffman et al have suggested that upregulation of NMDA receptors may lead to withdrawal seizures and enhanced susceptibility to excitotoxicity, which may explain the continuing damage described above (97).

A number of findings have been made in experimental models, which suggest links between aging and alcohol toxicity. Lipofuscin is generally considered to be a marker of aging in CNS neurons. Several groups have found an increase in intracellular lipofuscin deposition in hippocampal (98) and cerebellar neurons (99) of rats subjected to chronic alcohol consumption. This occurs through lipid peroxidation, which has been shown to increase with alcohol (ethanol) consumption in a dose-dependent fashion in brain homogenates (100). This mechanism may play a role in the neurotoxicity of alcohol.

MOLECULAR MECHANISMS OF ALCOHOL NEUROTOXICITY

Molecular mechanisms of damage caused by alcohol are beyond the scope of this paper, but there is work being done currently on metabolites of ethanol (acetaldehyde), fatty acid ethyl esters (generated by nonoxidative metabolism of ethanol) (101), excitotoxins (102), nitric oxide (103), free radicals (104), and changes in neurotrophins (95). Wide-ranging changes have been reported in alcohol-related brain damage with regard to receptors (7) and amino acid neurotransmitters (105). Links between alcohol and thiamin deficiency have been discussed throughout this paper, and it is important to emphasize that this linkage does not necessarily depend upon associated poor nutrition. There are a number of interrelated factors whereby the alcohol interferes with the absorption, storage, and metabolism of the thiamin and its active phosphate coenzyme derivatives (64). This creates a scenario wherein alcoholics are frequently at risk of developing thiamin deficiency and associated brain damage (WKS). There are many other factors that can play a role in the long-term effects of alcohol on the nervous system. It should be remembered that alcoholics are prone to recurrent head injuries, seizures are common, and there is a close link between alcohol and the sleep apnea syndrome (44).

SUMMARY

There is pathological evidence showing that alcohol per se causes damage to both gray matter and white matter. White matter damage is predominant and results in a reduction in brain volume. A component of the white matter loss appears to be reversible in some cases, given a significant period of abstinence. The structural explanation for the white matter change has yet to be elucidated, but most likely relates to a change in myelination. There is a relationship between the volume of white matter lost and alcohol intake. The gray matter damage appears to be regionally selective, but many areas of the

brain appear to be resistant to damage. Neuronal loss has been documented in the superior frontal association cortex, but not in other cortical areas that have been examined. The frontal damage correlates with clinical and radiological data. The only other groups of neurons that are selectively damaged are cerebellar Purkinje cells and neurons in 2 hypothalamic nuclei (supraoptic and paraventricular). Experimental data suggest that hippocampus and amygdala are vulnerable, but human data is still inconclusive. Similarly, there is still some debate with regard to the locus ceruleus. The basal ganglia, nucleus basalis, and brainstem serotonergic raphe nuclei appear to be spared. Data on thalamic nuclei is sparse, although there is no doubt that this area is frequently damaged in those alcoholics with additional WKS (thiamin deficiency). Thiamin deficiency accounts for a major component of the brain damage in alcoholics. Apart from neuronal loss, there are many dendritic and synaptic changes documented in alcoholics and in experimental animal models of alcohol toxicity. These, together with receptor and neurotransmitter changes, may account for the some of the cognitive and functional deficits. It is difficult to define the levels of alcohol that cause these changes, but most of the human studies have involved patients who drank at least 80 grams of alcohol per day over decades.

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