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Chapter 72

NMDA receptor, magnesium and alcohol disease

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Introduction

The major hazard of alcohol abuse is the development of alcohol dependence. The sequel of alcohol disease consists of a progression of clinical manifestations: chronic alcoholism, pre-delirium, delirium tremens (DT), and alcohol encephalopathy (AE). In the latter term we include the following entities: Korsakoff's psychosis, Wernicke's encephalopathy, alcoholic dementia, and a state of intellectual reduction which makes social adjustment impossible. These progressive stages of alcohol disease are accompanied by (1) a parallel decrease of serum omagnesium concentration (S-Mg), the lowest value being found in AE (on the basis of this evidence Stendig-Lindberg introduced magnesium treatment in AE which alleviated or arrested the disease[1]); (2) decrease in intracellular magnesium[2]; (3) increasing degree of cerebral damage histologically similar to that seen in experimentally induced magnesium deficiency[3].

Cerebral blood flow

Diminished cerebral blood flow was found in AE patients, in chronic alcoholics with psychological deficits and in DT patients, as well as in alcoholics with psychiatric symptoms[4-6]. The intracellular free magnesium concentration was found to be decreased by 57 per cent in cultured canine cerebral vascular smooth muscle cells exposed to ethanol[7]. Therefore we postulate that the reduction in the cerebral blood flow and the resultant ischaemic changes seen in alcoholics are due to the presence of magnesium deficiency.

Enhanced activation of NMDA receptor in magnesium deficiency

The NMDA receptor is a CNS receptor located mainly in the hippocampal region of the brain, and inhibited amongst others by ethanol and by Mg^{2+}. Inversely, magnesium deficiency causes enhanced activation of the NMDA receptor which allows for the influx of Ca through the activated NMDA receptor channel. This constitutes the mechanism by which neuronal damage, cerebral ischaemia and prolonged seizures take place[8]. The increased enzyme activities of γ-glutamyl transpeptidase (GGT), aspartate amino transferase (ASAT) and alanine amino transferase (ALAT), which are always raised in chronic alcohol ingestion, could indicate an increased formation of glutamate, one of the two excitatory amino acids which activate the NMDA receptor. We suggest that the cumulative cerebral damage seen in alcoholic disease is caused by the activation of the NMDA receptor due to magnesium deficiency and probable concurrent rise in glutamate.

Epileptogenic activity

Reduction of extracellular magnesium was found to induce epileptogenic events in rat neocortical slices by enhancing the activation of the NMDA receptors[8], while magnesium treatment in the form of various compounds is known to have anticonvulsant effects. In withdrawal syndromes the

epileptogenic tendency appears to be due to the compounded effects of magnesium deficiency and the withdrawal of the inhibitory effect of alcohol on the NMDA receptor.

Alcohol dependence

The majority of evidence gathered indicates that alcohol inhibits the NMDA receptor even in a relatively low concentration[9]. Ethanol and magnesium inhibit the NMDA receptor through two different mechanisms and in the absence of magnesium higher concentrations of ethanol are required to inhibit the receptor. We envisage that alcohol ingestion, to begin with, inhibits the NMDA receptors. With prolonged intake, a progressive decrease of the available magnesium follows. This opposes the inhibitory effect of ethanol and allows for excitation of the receptors. In the presence of growing magnesium deficiency the subject's need of alcohol increases to counteract enhanced activation of the NMDA receptors[10]. This mechanism offers a highly plausible explanation for the development of alcohol dependence. The recent experimental study of Lamblin *et al.*[11], which showed that in male rats rendered alcohol dependent oral magnesium administration decreased the alcohol dependence, strengthens our hypothesis.

Treatment and prevention of alcohol disease

Magnesium therapy in alcohol disease still appears to be a subject of controversy. A rationale for recommending magnesium therapy in chronic alcoholism is (1) its role in the regulation of the smooth muscle tone, including that of the vessel walls, that is, in safeguarding the cerebral circulation from vasoconstriction and resulting cerebral ischaemia, (2) prevention of enhanced activation of NMDA receptor, thereby protecting from cerebral damage and epileptogenic activity, (3) prevention of alcohol dependence.

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