The Effect of Acute and Repeated Hyperammonemia on \( \gamma \)-Glutamyl Transpeptidase in Homogenates and Capillaries of Various Rat Brain Regions

WOJCIECH HILGIER,¹ JAN ALBRECHT,*¹ VACLAV LISY,² AND FRANTISEK STASTNY²

¹Department of Neuropathology, Medical Research Centre, Polish Academy of Sciences, PL-00-784 Warsaw, Poland; and ²Institute of Physiology, Czechoslovak Academy of Sciences, CS-142-20 Prague, Czechoslovakia

Received January 10, 1990; Accepted May 31, 1990

ABSTRACT

The effect of hyperammonemia of varying degree and duration on the \( \gamma \)-glutamyl-transpeptidase (GGT) activity was studied in the homogenates and capillaries of different brain regions of the rat. "Acute" hyperammonemia (750 and 600 mg of ammonium acetate per kg b.w. were injected i.p. at 30 min interval, and the animals were decapitated immediately), in which blood ammonia was increased 14-fold, and brain ammonia six-fold above the control level, produced a 20% increase of the enzyme activity in cerebellum, and a 17% decrease in gyrus dentatus, but had no effect in the frontal cortex and the CA1 and CA3 regions of hippocampus. "Subchronic" hyperammonemia (two injections of 600 mg ammonium acetate/kg were given at 24 h intervals, and tissue samples were removed 24 h later), that was accompanied by only a 60% increase of blood or brain ammonia,

*Author to whom all correspondence and reprint requests should be addressed.
increased the activity in cerebellum to 38% above control, but produced no effect in the other brain regions. "Chronic" hyperammonemia (three injections of 600 mg ammonium acetate/kg at 24 h intervals and excision of tissue samples 30 min after the last injection), in which blood and brain ammonia were, respectively, 60 and 100% higher than in control animals, elevated the GGT activity in the cerebellum by 57%, in CA1 by 15%, and in CA3 by 21%, but produced no effect in the frontal cortex or gyrus dentatus. By contrast, "chronic" hyperammonemia produced a 30% increase of GGT activity in cerebral cortical capillaries, but only a 10% increase in hippocampal capillaries, and no change in cerebellar capillaries. The results suggest that, hyperammonemia of relatively long duration may contribute to the enhancement of brain GGT activity observed in chronic forms of hepatic encephalopathy. However, ammonia does not appear to activate the enzyme directly.

**Index Entries:** γ-Glutamyl transpeptidase; hyperammonemia; cerebral cortex; hippocampal formation; cerebellum; brain capillaries.

**INTRODUCTION**

Ammonia is a major neurotoxin, implicated in the pathomechanism of hepatic encephalopathy (HE) (Norenberg, 1986; Butterworth et al., 1987; Cooper et al., 1988). Increased ammonia entry into the brain is followed by an elevation of brain glutamine content in various brain regions (Hawkins et al., 1987; Butterworth et al., 1987; Bates et al., 1989). An increased Gln content is believed to be the factor that facilitates neutral amino acids transport across the capillary barrier, and leads to excess accumulation of tryptophan and other aromatic amino acids in HE (James et al., 1978; Cardelli-Cangiano et al., 1981; Bachman and Colombo, 1983). The concept that γ-glutamyltranspeptidase (GGT) participates in this transport system (Samuels et al., 1978; Gorgievski-Hrisoho et al., 1986), prompted us to examine the enzyme activity in HE. Our previous study revealed that GGT becomes elevated in the thioacetamide (TAA)-induced HE model (Stasny et al., 1988). However, since toxic liver damage is followed by accumulation in the brain of a variety of neurotoxins (Zieve, 1987), the role of ammonia in GGT activation remains unclear. Therefore, in this study, we have concentrated on the effects of simple hyperammonemia of different degree and duration on the GGT activity in various brain regions, and in brain capillaries.

**METHODS**

**Models of Hyperammonemia**

Adult female Wistar rats, weighing 160–220 g, were given i.p. injections of ammonium acetate in the three following ways. One group was treated first with a 750 mg/kg dose, that was followed after 30 min by a