REGULATION OF GLUTAMATE DEHYDROGENASE DURING POSTNATAL DEVELOPMENT OF MICE

ABSTRACT

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Introduction

Glutamate dehydrogenase occupies a central role in nitrogen and carbon metabolism in practically all organisms. The reaction which it catalyses feeds the tricarboxylic acid cycle with carbon intermediate necessary for generating energy as well as precursors for other biosynthetic purposes such as in gluconeogenesis. GDH is also considered as an accessory enzyme to the urea cycle because of its involvement in NH_4^+ metabolism. It also plays an important role in the metabolism of the excitatory neurotransmitter glutamate in the central nervous system signifies the potential of this enzyme in influencing a wider aspect of metabolism in higher organisms, have gathered significant attention. However, its role in the development and/or aging of organism has not been adequately explored.

This study aims to determine the tissue distribution of GDH in mice at different postnatal ages and to gain insight into its regulation by various hormones at different postnatal ages. Further, this enzyme was purified from immature and matured ages to determine if any changes occur in its physico-chemical properties during the course of postnatal development.

Age and tissue distribution

GDH exhibited an age- and tissue-specific pattern of distribution in terms of activity with the highest activity observed in the liver, followed by the kidney, brain and heart. Except for the brain, which showed a gradual increase in activity with age, GDH from the liver, kidney and heart exhibited peak activity during the first 10 days after birth which declined to a more or less stable adult level after 30 days postnatally.

Hormonal responses

Administration of hormones to the immature and matured animals point towards an age- and tissue-specific pattern of response. Thus, it was observed that, T_3 administration resulted in 2.5 fold increase in GDH activity in the heart of the immature mice as compared to the mature mice which exhibited no response to this hormone. Whereas, dexamethasone treatment exerted response in the heart tissue of matured mice only. The brain tissue showed an overwhelming response to T_3 administration in terms of GDH activity with the immature mice exhibiting an excess of 2 fold over its matured counterpart and dexamethasone treatment evoked response only in the matured animal. T_3 administration also resulted in significant increase in GDH activity in the kidney and liver with the matured animals showing higher induction than the immature mice. Dexamethasone treatment however, induced similar responses in both the liver and kidney tissues with an approximately 2 fold increase in GDH activity for both the ages studied. Testosterone administration alone did not exert any significant changes in all of the tissues at both ages studied. Treatment with hormone combinations also resulted in differential response in the various tissues at the two ages. Thus, dexamethasone-triiodothyronine (dex-T_3) administration resulted in a significant 4 fold increase in GDH activity in the heart of the immature mice only with respect to the control, whereas testosterone-T_3 (test-T_3) treatment did not evoke any significant enhancement of GDH activity in this tissue at both the ages studied. In the brain, dex-T_3 administration resulted in a significant synergistic increase (5 fold) of GDH activity in the immature mice however; it was apparently antagonistic in the matured animal. Test-T_3 combination treatment exerted higher increase of GDH activity of the immature compared to the matured mice. In the kidney, dex-T_3 combination

treatment resulted in significant increase (3 fold) of GDH activity in the matured mice compared to the 1.7 fold increase in the immature mice. A moderate (1.6 fold) increase in GDH activity was observed in this tissue of the matured mice in response to test-T_3 administration. The liver tissue also exhibited a synergistic response to dex-T_3 treatment with a 2.8 fold increase in enzyme activity of the immature mice and 4 fold increases in the mature mice. Test-T_3 treatment also showed similar synergistic response vis-à-vis enzyme activity in the adult mice, however no significant response was observed in the immature mice in this tissue.

Physico-chemical comparison of GDH

The physico-chemical properties of dialysed GDH from immature and matured mice indicated that there was no alteration in terms of buffer ionic optima, pH and temperature stability. The enzyme from both the ages also showed an overall similar pattern of response to the effect of various co-substrates and co-enzymes. Inhibition and inactivation studies on the enzyme did not reveal any significant differences between the two ages and further comparison of the total and subunit mass also showed no differences. However, the only difference observed was in the kinetic behaviour of the enzyme towards its substrate; α-ketoglutarate with the matured mice showing higher K_m, compared to its immature counterpart. The antigenic property of glutamate dehydrogenase from the liver of immature and matured mice from both the ages remained unchanged.

In conclusion, this study has given some insight into the endogenous activity of GDH which was marked by age- and tissue-specific pattern of distribution and have also indicated the larger role played by hormones like T_3 and dexamethasone in the regulation of this enzyme.