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Pregnancy Associated Plasma Protein-A and Epilepsy

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Abstract: In this study, we aimed to investigate the role of pregnancy-associated plasma protein-A (PAPP-A) as insulin-like growth factor binding protein-4 (IGFBP-4) protease in epilepsy patients. We studied 16 epilepsy patients and 10 healthy controls. Serum PAPP-A levels of epilepsy patients (6.8 ± 3.2 mU/L) were higher than of the control group (5.1 ± 1.9 mU/L), but the difference was not statistically significant (P > 0.05). We concluded that PAPP-A may increase the bioavailability of insulin-like growth factors (IGFs) due to decreased neurogenesis and synthesis of IGFs in chronically epilepsy patients.

Key Words: Brain tumor, epilepsy, IGF-I, IGFBP, IGFBP-4, neurogenesis, PAPP-A

Gebelikle İlişkili Plazma Protein-A ve Epilepsi

Özet: Bu çalışmada insulin benzeri büyüme faktörü bağlayıcı protein-4 (IGFBP-4) proteaz olarak bilinen gebelikle ilişkili plazma protein A'nın (PAPP-A) epilepsili hastalardaki rolünü araştırmayı amaçladık. Çalışmaya 16 epilepsi hastası ve 10 sağlıklı birey alındı. Epilepsili hastalarda serum PAPP-A düzeyleri (6,8 ± 3,2 mU/L) kontrol grubuna göre (5,1 ± 1,9 mU/L) yüksek bulunmasına rağmen aradaki fark istatistiksel olarak anlamlı bulunmadı (P > 0.05). PAPP-A'nın epilepsili hastalarda azalan insülin benzeri büyüme faktörlerinin (IGF) sentezi ve nörogenez durumunda IGF'lerin etkinliğini artırmada rol alabileceğini düşünmekteyiz.

Anahtar Sözcükler: Beyin tümörü, Epilepsi, IGF-I, IGFBP, IGFBP-4, Nörogenez, PAPP-A

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Introduction

The insulin-like growth factor (IGF) axis is a multi-component network of molecules that is ubiquitously involved in the regulation of growth, proliferation, and differentiation of a variety of cell types. This axis includes two major ligands, IGF-I and IGF-II, the type 1 and type 2 IGF receptors, a family of at least six high-affinity IGF binding proteins (IGFBPs) that determine the bioavailability of IGFs, and a group of IGFBP proteases that cleave IGFBPs and hence modulate the bioavailability of IGFs (1).

IGF-dependent IGFBP-4 protease activity has been described in a variety of cells, including fibroblasts, osteoblasts, endometrial stromal cells, and granulosa cells (1). The IGF-dependent IGFBP-4 protease has been postulated to amplify local IGF-I activity in wound healing, vascular repair, bone remodeling, and development of the dominant follicle (2). IGFBP-4 protease was purified from human fibroblasts and identified as pregnancy-associated plasma protein-A (PAPP-A) (2).

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During pregnancy, PAPP-A is produced in high concentrations by trophoblasts, and maternal serum assessment between 11 and 14 weeks of gestation has significant utility in screening for Down syndrome (DS) and other chromosomal anomalies. In addition to pregnancy, the clinical value of PAPP-A continues to grow as new data become available.

It has been reported that the occurrence of epilepsy in DS in childhood is not different from that in the general population, but infantile spasms are prevalent in DS (3). However, in adult DS patients, epilepsy is more common than in the normal population and the possible mechanisms have not been adequately explored (4). In the present study, we aimed to search the role of PAPP-A as IGFBP-4 protease in epilepsy patients.

Blood samples were drawn from the antecubital vein from 16 epilepsy patients (9 men and 7 women, mean age 36 ± 11 years) and from 10 control subjects (7 men and 3

women, mean age 29 ± 8 years). Blood samples were collected in sterile tubes without additives and centrifuged at 1500 x g for 10 min in 1 hour. Following centrifugation, the serum aliquots were stored at -20°C until analysis. All samples were processed within 1 month. Serum PAPP-A levels were determined by an ultrasensitive enzyme-linked immunosorbent assay (ELISA) (Diagnostic Systems Laboratories, Texas-USA). The minimum detection limit of the method was 0.24 mU/L and the coefficient of variation (CV) was 4.80%.

Data were expressed as the mean ± SD. The un-paired Student's t test was used to evaluate the significance of difference between epilepsy (all patients) and control groups. Values of $P < 0.05$ were considered as statistically significant.

Serum PAPP-A levels of epilepsy patients (6.8 ± 3.2 mU/L) were higher than of the control group (5.1 ± 1.9 mU/L), but the difference was not statistically significant ($P > 0.05$).

Discussion

IGFs regulate both normal and malignant brain growth and promote the proliferation of oligodendrocytes and myelin synthesis (5). IGFs are also anabolic regulators in astrocytes and neurons. Specific receptors for IGFs are found in central nervous system (CNS) tumors, and various IGFBPs are also secreted by these tumors (6).

Among the six IGFBPs, IGFBP-4 is unique in inhibiting IGF actions (7). PAPP-A, as IGFBP-4 protease, degrades IGFBP-4 and increases the local concentration and consequently the bioavailability of IGF-I (2). PAPP-A is also potentially proatherosclerotic, and high serum levels have been observed in patients with acute coronary syndromes (8). It has been shown that status epilepticus and hippocampal injury induce new neuron production in the dentate gyrus (9). However, Hattiangady and co-workers (10) have demonstrated that a chronically epileptic hippocampus has 53% less IGF-I in comparison to the adult intact hippocampus. In the present study, no patient was in status epilepticus when blood was drawn for PAPP-A. Jacoby and co-workers (11) have demonstrated that homozygous Galr1-/- mice have reduced circulating IGF-I and exhibit spontaneous tonic-clonic seizures. Systemic administration of kainic acid evokes acute seizure in the hippocampal pathway that resembles temporal lobe epilepsy. Kar and co-workers (12) have shown that administration of kainic acid decreased IGF-I transiently in almost all regions of the hippocampus. Taken together, it seems that epilepsy, especially temporal lobe epilepsy, is accompanied with low IGF-I serum levels and the IGF axis and related molecules may play an important role in the pathophysiology of epilepsy. We concluded that, in spite of not being statistically significant, elevated PAPP-A in epilepsy patients may increase the bioavailability of IGFs due to decreased neurogenesis and synthesis of IGFs in chronically epileptic patients. However, this hypothesis needs further studies.

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