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Original Article

Diabetes Mellitus Type1 and Neuronal Degeneration in Ventral and Dorsal Hippocampus

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ABSTRACT

Background and Objectives: **Studies have documented the morhplogical, neurochemical and functional difference between the dorsal and ventral zones of hippocampus. The aim of this study was to assess the effects of chronic diabetes mellitus type1 on ventral and dorsal zones of hippocampus.**

Methods: **Experimental diabetes was induced by stereptozotocin at a dose of 60 mg/kg. At the end of 8 weeks the brains were removed and stained by cresyl violet. The number of dark neurons in CA1 and CA3 regions of dorsal and ventral zones of hippocampus was counted by modified stereological method.**

Results: **The number of dead neurons in CA3 ventral showed significant level of difference ($P<0.05$) in comparison to CA3 dorsal. The number of dead neurons in CA1 ventral and CA1 dorsal showed also significant difference ($P<0.05$)**

Conclusion: **The results of our study Provide evidence that is indicative of more vulnerability of ventral zone than dorsal zone of hippocampus to diabetes mellitus type 1.**

Keywords: **Type 1 Diabetes Mellitus, Hippocampus, Neuron Degeneration, Rat**

Introduction

Hippocampus is the central part of limbic system which its role in memory and learning has been well documented. Structurally hippocampus is divided into two interlocking parts, hippocampus proper or cornu amonis (CA) and dentate gyrus. Functionally the hippocampus is segmented into dorsal and ventral parts. The ventral (anterior in primates) relates to stress, emotion, and affect. The dorsal hippocampus (posterior in primate) correlates

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with cortical regions involved in information processing (1, 2). Several studies have documented functionally difference between dorsal and ventral hippocampus based on lesion experiments (3). Structural complexity of hippocampus makes it vulnerable to many metabolic disorders like diabetes mellitus type1. At present central nervous system (CNS) complications of diabetes mellitus type1 are well known. For instance diabetes mellitus type1 is associated with increased risk of cerebrovascular accident (CVA) and Alzheimer disease (4).

Among the CNS regions the hippocampus is the most sensitive regions to diabetes mellitus (5). Experimental and neuroimaging studies have shown a wide range of neuropathological changes in CNS of diabetic cases specifically in hippocampus. Magarinos reported that diabetes mellitus type 1 as an endogen stressor causes mossy fiber necrosis and simplification/retraction of CA3 apical dendrites (6). Additionally electrophysiological abnormalities, suppressed cell proliferation in dentate gyrus and apoptosis have been reported (7). We previously reported that STZ-induced diabetes accelerates dark neuron formation in the CA3 and the dentate gyrus (7, 8). Among these neuropathological changes, neuronal death has been noticed because of its central role in diabetes–related central neuropathy (6-9). Most experimental works have reported the neuronal death in dorsal zone of hippocampus in particular CA1 and CA3 and considered the hippocampus as a homogenous (10) and the structural and functional differences of dorsal and ventral hippocampus has been neglected. On the other hand a vast majority of studies have documented the morphological, neurochemical and functional difference between the dorsal and ventral zones of hippocampus (11-13).

Given that CA1 and CA3 regions are the main regions of cornu amonis involved in memory processing, forming major internal and external circuits of hippocampus (14) and by taking into consideration these differences especially functional we hypothesized their response in presence of metabolic insults such as hyperglycemia would be different. We aimed to evaluate the effects of chronic hyperglycemia on the rate of neuronal death, as a main leading cause of central and periphral neuropathies in ventral and dorsal zones of hippocampus.

Materials and Method

This study was carried out on male Wistar rats (age 120 day, body weight 240–260 g, n=10). All rats maintained in animal house and allowed free access to drinking water and standard rodent diet. Experiments performed during the light period of cycle and conducted in accordance with Regional Committee of Ethic complied with the regulations of the European Convention on Vertebrate Animals Protection (2005). We considered fasting blood glucose (FBG) >250 mg/dL as a diabetic. Diabetes mellitus type 1 was induced by a single intraperitoneal (IP) injection of STZ (Sigma Chemical,St. Louis, Mo) at a dose of 60 mg/kg dissolved in saline (control animals were injected with saline only) (7). Four days after the STZ injection, FBG was determined in blood samples of tail veins by a digital glucometer (BIONIME, Swiss). In the end of eight weeks, the animals were anesthetized and the harvested brains were post-fixed for two weeks.

Serial coronal sections (thickness 10 μm) were made through the entire extent of hippocampus and stained with cresyl violet (Sigma Chemical,St. Louis, Mo) (8). The number of dead neurons of CA1 and CA3 in both dorsal and ventral zones were counted according to modified stereological rules (7).

Statistical Analysis

All data are expressed as mean ± SD. Statistical comparison for the number of dead neurons of CA1dorsal/ventral and CA3 dorsal/ventral zone was made using *t*-test. Statistically significant difference was accepted at the $P<0.05$ level.

Results

The number of dead neurons in CA3 ventral (91.5±17) and CA3 dorsal (36±19) showed significant level of difference (P<0.05) (Fig.1). The number of dead neurons in CA1 ventral (77±33) and CA1 dorsal (12±9) showed also significant difference (P<0.05) (Fig. 2). Dead neurons were not seen in control group.

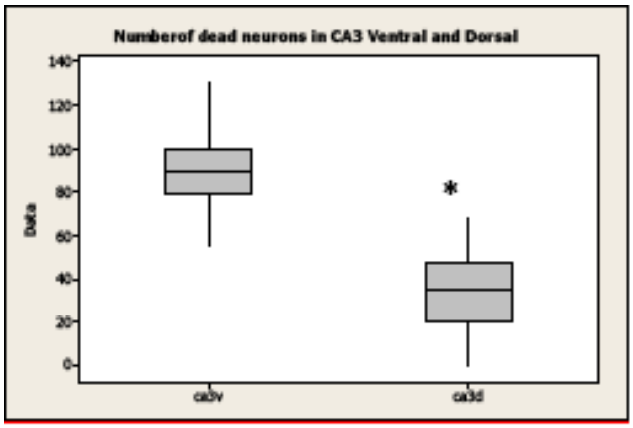

Fig.1: the number of dead neurons in CA3 region of ventral (ca3v) and dorsal (ca3d) zones. The deference between the number of dead neurons was significant. (P<0.05)

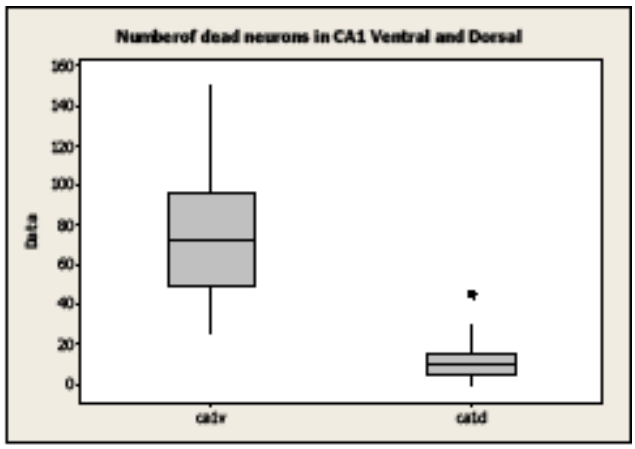

Fig. 2: The number of dead neurons in CA1 region of ventral (ca1v) and dorsal (ca1d) zones. The deference between the number of dead neurons was significant. (P<0.05)

Discussion

CA1 and CA3 of the hippocampus contain pyramidal shape neurons which receive afferents from the mossy fibers of dentate gyrus. Strictly speaking granular cells of the dentate gyrus send their glutamergic mossy endings to CA3 region. CA1 pyramidal neurons receive collateralls from CA3 pyramidal neurons which in turn makes one of the main internal neuronal circuits of memory process (15).

The results of this study showed that the rate of neuronal death in CA1 and CA3 region of ventral zones progress more rapidly than those of dorsal hippocampus. In other word the response of dorsal and ventral segments of hippocampus in diabetic paradigm is different and the ventral zone would be more vulnerable and sensitive to diabetes mellitus type1. To the best of our knowledge the comparison between the vulnerability of different zones of the hippocampus in presence of diabetes mellitus type 1 has not been mentioned before. Previous researches have shown that diabetes mellitus type1 accelerates the rate of neuronal degeneration inCA1 and CA3 regions of hippocampus in diabetic animals (6-9) and a wide interconnected ranges of factors such as increased oxidative stress, free radical generation, glutamate excitotoxicity and increased level of circulating glucocorticoids are contributed in neuronal death (6,8). Regardless the mentioned factors, neurodegenration can be indicative of accelerated brain aging process in diabetes. Severe rate of neurodegenration in ventral zone can also be interpreted as regional cellular difference resulted from, gene expression, morphological, functional, firing characteristics and neural connection differences between dorsal and ventral hippocampus which have been reported by other authors (10-13, 16).

One of the proposed mechanisms for neurodegenration in diabetes is glutamate exctotoxicity (6). Glutamate is the main neurotransmitter in internal circuits of hippocampus necessarily in synaptic transmission and plasticity (17, 18). Glutamate excitotoxity is considered as main leading cause of dark neurons formation (19). Ventral hippocampus involves in emotional reactions

like fear and anxiety and higher rate of neuronal lose resulted from hyperglycemia may impose adverse effects on its functions and in developing of psychiatric disorders (20, 21). Although ventral segment contains lower levels of NMDA, AMPA mRNA and receptor densities compared with dorsal segment, it may reflect the lower ability of ventral segment for synaptic plasticity (18). It can be assumed lower plasticity ability of ventral segment may predispose this zone more vulnerable to insults such as hyperglycemia and subsequently increase in neuronal death.

Conclusion

Our results are in line with recent works question the homogenous entity of hippocampus. In other words different response of the dorsal and ventral segments to hyperglycemia indicates the selective vulnerability of the cornu amonis. We recommend more studies to reveal the consequence of ventral hippocampus neurodegeneration on cognitive performances of diabetic cases.

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