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Predictive value of early decreased plasma ghrelin level for three-month cognitive deterioration in patients with mild traumatic brain injury

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ABSTRACT

The orexigenic hormone, ghrelin, is tightly linked to cognition impairment in neurodegenerative disorders. No previous studies have investigated the early ghrelin concentration change in patients with mild traumatic brain injury (mTBI) and it's relationship to cognitive deterioration. This study was performed to investigate the early plasma ghrelin concentrations in patients with mTBI and to explore the relationship between ghrelin and cognitive deterioration. Plasma ghrelin concentrations of 118 adults after acute mTBI were determined by enzyme-linked immunosorbent assay. Forty patients (33.9%) had cognitive deterioration three months after mTBI. Plasma ghrelin levels were significantly lower in mTBI patients with cognitive deterioration than patients without cognitive deterioration (38.8 ± 4.5 pg/mL vs 50.8 ± 7.7 pg/mL, $P < 0.001$). Decreased Plasma ghrelin level was identified as an independent predictor for three-month cognitive deterioration after mTBI (odds ratio, 0.746; 95% confidence interval, 0.651–0.856; $P < 0.001$). Plasma ghrelin level was negatively associated with serum adrenocorticotrophin hormone level ($t = -6.854$, $P < 0.001$) and age ($t = -6.112$, $P < 0.001$). A plasma ghrelin level of 41.6 pg/mL predicted three-month cognitive deterioration after mTBI with the optimal sensitivity (85.9%) and specificity (80.0%) values (area under curve, 0.904; 95% confidence interval, 0.852–0.957; $P < 0.001$). The predictive value of ghrelin was bigger than that of serum adrenocorticotrophin hormone level (area under curve, 0.638; 95% confidence interval, 0.536–0.741; $P = 0.014$) and age (area under curve, 0.638; 95% confidence interval, 0.536–0.741; $P = 0.014$) for three-month cognitive deterioration after mTBI.

1. Introduction

Ghrelin, a novel "gut-brain" hormone, is a multifunctional 28-amino acid (aa) hormone produced in stomach as well as a wide variety of tissues, including the brain, where it can act as a paracrine/autocrine factor [27]. It was firstly identified as an endogenous ligand for the growth hormone secretagogue receptor type 1a (GHSR-1a) and was reported to induce growth hormone (GH) release through pituitary GHSR-1a stimulation [1,8,25,32]. Though the relative contribution of ghrelin derived from nongastric sources in the circulation and its physiological function are unknown, it is noticeable that GHSR1a is detected mostly abundant in the pituitary gland and hypothalamus [14,34].

Actually, ghrelin is tightly associated with the adjustment of hypothalamus pituitary axis (HPA) hormones secretion and often receives feedback from HPA hormones. Besides strong stimulation of GH secretion, ghrelin secretion also receives negative feedback from GH/IGF-I axis [8,11]. Ghrelin significantly stimulates lactotroph and corticotroph secretion, all these actions depend on acylation of ghrelin in serine-3 that allows binding and activation of the GHS-R1, and is generally sensitive to the negative glucocorticoid feedback [13]. Ghrelin suppresses secretion of LH, FSH and TSH [23,24] while testosterone and estrogen directly induce ghrelin expression and production [20,36]. Esterification of the hydroxyl group of the Serine-3 residue of ghrelin by n-octanoic acid increases the hydrophobicity of the ghrelin molecule, and appears to be essential for the activity of ghrelin in both rats and humans [3].

Hypothalamus pituitary axis has long been reported playing a important role in stress related physiological disorders such as posttraumatic stress disorder (PTSD) which often accompanied

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with cognitive impairment [12,35]. Meyer reports a ghrelin-growth hormone axis may drives stress-induced vulnerability to enhanced fear [30].

The relationship between cognitive impairment and ghrelin in patients with mild traumatic brain injury (mTBI) is currently unknown. Given that researches suggest a link between ghrelin-hypothalamus pituitary axis hormone and stress induced cognitive impairment, we investigated the predictive value of early changed plasma ghrelin level for three-month cognitive deterioration in patients with mTBI.

2. Materials and methods

2.1. Study population

The inclusion period was from October 2010 to August 2013. One hundred and fifty consecutive patients aged 18–65 with a well-documented clinical history of mTBI within five days were prospectively recruited from neurosurgery department of First Affiliated Hospital of Zhejiang Chinese Medicine University and Affiliated hospital of Hebei University. The mTBI was diagnosed according to the definition developed by the ACRM [26]: that a person with mild TBI was one who had traumatically induced changes as manifested by at least one of the following: 1. Any period of loss of consciousness (LOC) for less than 30 min and a Glasgow Coma Scale score of 13–15. 2. Any posttraumatic amnesia (PTA) immediately before or after the accident and not exceeding 24 h. 3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused). 4. Focal neurological deficits.

Exclusion criteria were: multiple injuries, a history of traumatic brain injury, a history of other neurologic diseases, psychiatric disturbance, educational period less than 9 years, presence of other prior systemic diseases and brain contusion or laceration demonstrated by CT scan. Accordingly, 4 patients were excluded due to history of other neurologic disease, 8 patients with a small brain contusion, and 20 with a less than 9 years educational history. The remaining 118 patients were included in our study. Informed consent in this study was obtained from participator. This protocol was approved by the Ethics Committee.

2.2. Demographic, clinical and laboratory material assessment

Demographic variables included were: age, sex, average years of schooling, academic degree and body composition markers (i.e. body mass index and waist-to-hip ratio). Clinical and laboratory variables included were: loss of consciousness (LOC), Glasgow Coma Scale score (GCS) on admission, posttraumatic amnesia (PTSA), alteration in mental state, focal neurological deficits, blood glucose level on admission, blood cholesterol on admission, blood pressure, blood white blood cell count, blood red cell count, blood platelet count, plasma ghrelin level, history of smoking or alcoholism and serum hypothalamus pituitary axis hormones. A history of smoking was defined as consecutive cigarettes consumption two years prior to the mTBI and more than two packs one month [10]. Alcoholism was based on the use of alcohol one month prior to the mTBI. Patients included in the group of preinjury alcohol abuse had a alcohol consumption more than five drinks a week for men and more than four drinks a week for women [9]. At admission, clinical severity was assessed. All computerized tomography(CT) scans were performed according to the neuroradiology department protocol.

2.3. Neurocognitive testing

The Neurocognitive evaluation was based on following tests for Adult-Chinese devised edition performed on admission and three months after mTBI. 1. Concept Shifting Test (CST): the CST is adapted from the Trail Making Test, which is a test of visual conceptual and visuomotor tracking and has been used to measure the ease of shifting between concepts in ongoing behavior [19]. 2. Stroop Color Word Test (SCWT): the SCWT is often used to evaluate selective attention, mental speed, and interference susceptibility [19]. 3. Visual Verbal Learning Test (VVLT): the VVLT is a visual version of the Rey Auditory Verbal Learning Test and often used to evaluate the memory capability [29]. 4. Fluency: this test is used to measure the adequate, strategy-driven retrieval of information from semantic memory [22]. 5. Letter Digit Substitution Test (LDST): this test is an adaptation of the procedurally identical Symbol-Digit-Modalities Test and is used to measure the speed of processing of general information [22,29]. 6. The Motor Choice Reaction Test (MCRT): this test is a computer task in which reaction time is studied as a function of the complexity of the task requirement [18].

2.4. Ghrelin and hypothalamus pituitary axis hormones detection

Serum ghrelin levels were detected in the first three day after recruitment using the Linco Research Human Ghrelin (active) enzyme-linked immunosorbent assay kit, a quantitative procedure with ghrelin sensitivity of 10 pg/ml. Specimens were stored at −80 °C until assayed. Manufacturer's directions were followed and acidified specimens (final concentration of 0.06 N HCl) were tested in duplicate.

During the first three day, mTBI subjects had daily morning measurements of serum growth hormone (GH), insulin-like growth factor-1 (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH). The first hormone levels were drawn within 24 h of admission, with subsequent draws occurring at 6–7 am up to post-admission day 3.

As previously described, serum adrenocorticotropic hormone (ACTH) and cortisol levels were also drawn within 24 h, with subsequent twice-daily draws occurring at 6 am and 4 pm [7].

Serum GH was measured by an enzymatically amplified two-step sandwich-type immunoassay with reagents obtained from Diagnostic Systems Laboratories. Serum IGF-1 and TSH were measured by RIA kits from Quest Diagnostics. Serum FSH and LH were measured by fluoroimmunometric assays with reagents provided by Delfia. Serum total ACTH and cortisol were measured by RIA using reagents from Diagnostic Products Corporation after extraction.

2.5. Statistical analyses

Statistical analysis was performed with IBM SPSS Statistics 21.0. The normal distribution of data with the sample size more than fifty was assessed by the Kolmogorov–Smirnov test, or else Shapiro–Wilk was used when a sample size was less than fifty. All values were expressed as median (lower quartile, upper quartile), mean ± SD, or counts (percentage) unless otherwise specified. X^2 test or Fisher's exact test, unpaired Student's t test and Mann–Whitney U test were used for comparisons of categorical data, continuous normally distributed variables and continuous non-normally distributed variables accordingly. The relationship between ghrelin and other variables was determined by Spearman's or Pearson's correlation coefficient and multivariate linear regression. The correlation of ghrelin to cognitive deterioration was assessed in a logistic regression model. For multivariate analysis, we included the significantly different outcome predictors as assessed in univariate analysis. Receiver operating characteristic curve was configured to establish the cutoff point of ghrelin with