行政院國家科學委員會補助專題研究計畫成果報告

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※　男性脊髓損傷患者血清瘦素與身體質量指數　※

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計畫編號：NSC 89－2314－B－002－448

執行期間：89 年 08 月 01 日至 90 年 07 月 31 日

計畫主持人：王顏和

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一、中文摘要

脊髓損傷除了影響神經功能外，也會造成各種內分泌之變化，包括周邊內分泌器官及下視丘—腦垂體軸之變化。也就是說，中樞神經系統損傷會影響內分泌的功能。但是，瘦素在脊髓損傷患者的血清濃度變化，及其與其他激素的關係，卻很少受到重視。在本研究，我們嘗試證明我們的假設，就是脊髓損傷後的交感神經失神經作用、反覆感染、以及可能的中樞神經傳導物質與脊髓損傷患者的血清瘦素濃度改變有所關聯。

在本研究我們將探討男性脊髓損傷患者血清瘦素與身體質量指數及各種激素之相關性。這橫斷性研究計畫將在我們大學附設醫院執行，它是一所三級轉診中心。我們研究的對象包括 47 位外傷性完全性脊髓損傷男性患者，另 47 位年齡與身體質量指數相稱之健康男性。每一位脊髓損傷患者以放射免疫法測定其血清四碘甲素、三碘甲素、甲促素、乳促素、生長激素、似胰島素第一因子、濾胞促素、黃體促素、睪固酮與血漿皮促素，而兩組受測者皆測定血清瘦素、皮醇與身體質量指數。

結果發現脊髓損傷患者血清瘦素明顯高於對照組，而在兩組都可見血清瘦素與身體質量指數呈線性關係。在脊髓損傷患者，血清瘦素與身體質量指數呈現多次方關係，在較低身體質量指數部份可見 J 現象。另在脊髓損傷患者血清皮醇與血清呈現明顯相關。

總之，脊髓損傷後所帶來的交感神經失神經作用、周邊神經麻痺、反覆感染、以及可能的中樞神經傳導物質改變都可能造成男性患者血清瘦素值增高。
關鍵詞：脊髓損傷、中樞神經傳導物質、瘦素、下視丘—腦垂腺—內分泌軸、身體質量指數

Abstract

Spinal cord injuries (SCI) can cause various hormonal changes. The pathomechanisms include peripheral endocrine organ dysfunction and central regulatory disorders. It means that the impairment of central nervous system will affect the endocrine function. However, the change of serum leptin level in SCI, as well as its relationship to the other various hormones, have received little attention. In this study, we try to verify our hypothesis that sympathetic denervation, recurrent infections as well as possible central neurotransmitter alterations after SCI may contribute to the change of serum leptin level in men with SCI.

The objective of this project is to investigate the relationship among serum leptin, body mass index (BMI) and various hormone levels in men with spinal cord injury. A cross-sectional design was used. The setting is in a university hospital, a tertiary referral center. The participants included 47 men with traumatic neurologically complete SCI and 47 age- and BMI-matched male controls. In main outcome measures, various baseline hormone levels, included T_4, T_3, TSH, prolactin, GH, IGF-1, FSH, LH, testosterone and ACTH were measured in subjects with SCI; serum leptin and cortisol levels and BMI were measured in both groups.

The results: serum leptin was significantly higher in the group with SCI than in the control group. A linear relationship was found between serum leptin and BMI in both groups separately. A polynomial relationship was found between the serum leptin level and the BMI in the group with SCI. A "J" phenomenon is noted at the lowest BMI. Serum cortisol correlated significantly with serum leptin level in the group with SCI.

In conclusion, sympathetic denervation, peripheral nerve palsy, recurrent infections, as well as possible central neurotransmitter alterations after SCI may contribute to the elevation of serum leptin level in men with SCI.
Key words: spinal cord injury, central neurotransmitter, leptin, hypothalamus-pituitary-endocrine axes, body mass index

二、緣由與目的

Leptin, the protein product of the ob gene, is an adipocyte-derived hormone and is shown to regulate body weight and adipose tissue mass through a feedback mechanism[1,2]. Apart from signaling energy reserves to the brain, leptin also plays an important role in regulating the hypothalamus-pituitary function[1-3]. Thus, quantitative or functional leptin deficiency due to mutations of the ob gene or leptin receptor gene results in early-onset morbid obesity, no pubertal development and dysfunction of gonadotropin, growth hormone and thyroid axes[4,5]. The hypothalamus-pituitary adrenal (HPA) axis of these patients remains to be studied in detail. In addition, serum leptin levels are related to the minute-to-minute changes in adrenocorticotropin (ACTH) and cortisol in normal men[6,7] and to the luteinizing hormone and estradiol levels in normal women[8].

Spinal cord injury (SCI) in men may result in various hormonal changes[9,10]. A large proportion of men with SCI was found to have abnormal pituitary hormone responses to hypothalamic releasing hormones[11-13]. It is proposed that there may be alterations of central neurotransmitters after chronic SCI[11-13]. Also, an increase of body fat in subjects with SCI has been shown by various measurements such as bioelectrical impedance[14], isotope dilution[15], hydrostatic weighting[16] and dual-energy X-ray absorptionmetry[17,18]. In this study, we addressed the relationship between the serum leptin levels and the body mass index (BMI) in 47 male subjects with traumatic SCI (31 with tetraplegia and 16 with paraplegia) and 47 BMI-matched normal male controls (their age ranged from 22 to 59, mean 37.0, years), as well as the association between serum leptin with various hormone levels in the SCI group. The age of SCI group ranged from 21.6 to 60.3 years with a mean of 36.5. Intervals between their injuries and this study varied from 1.0 to 35.3 years with a mean of 9.1. The level of injury varied from C_3 to L_1 and all lesions were complete. The BMI varied from 14.5 to 29.4 kg/m^2 with a mean of 20.9.

After a thorough discussion of the purpose and design of the study, all subjects assented voluntarily to participate. All subjects, including healthy controls, had blood withdrawn between 8 and 9 AM after an overnight fast. All of the hormones were assayed by commercial RIA kits: T_4, T_3, TSH, FSH, LH, prolactin, cortisol, ACTH, GH, IGF-1, testosterone and leptin.

三、結果與討論

Serum leptin was significantly higher in the group with SCI than in the control group (6.23 ± 0.66 vs 3.07 ± 0.31 ng/ml, $P < 0.0001$). Serum leptin levels were higher for any given BMI value for those with SCI than for the controls.

A linear relationship was found between the serum leptin and the BMI in both groups separately (SCI: $r = 0.664$, $p < 0.0001$; Control: $r = 0.791$, $p < 0.0001$). A non-linear relationship was found between the serum leptin level and the BMI in the group with SCI only ($r = 0.752$, $p < 0.0001$; Leptin = 0.11 BMI^2 – 3.80 BMI + 38.01). A "J" phenomenon is noted at the lowest BMI.

Serum cortisol and T_4 concentrations were correlated significantly with the serum leptin level (Cortisol: $r = -0.36$, $p = 0.0142$; T_4: $r = -0.44$, $p = 0.0034$) in SCI subjects. After adjustment of the BMI effect, the correlation between serum leptin and T_4 became borderline ($p = 0.0854$). However, the cortisol effect still persisted independently ($p = 0.0260$). The best fitting model is as follows: [leptin] = 3.00 + 3.34 x [GP] – 0.10 x [GP] x [cortisol] + 0.58 x [BB] + 0.10 x [GP] x [BB]^2. GP: Group effect, SCI = 1, Normal control = 0. BB: centered BMI = BMI – 21.0. Centering in polynomial regression can substantially reduce collinearity .

Serum leptin was not significantly different in the paraplegics from that of the tetraplegics (7.46 ± 1.10 vs 5.59 ± 0.81 ng/ml, $p = 0.0608$). The serum concentrations of LH and FSH were significantly higher in the tetraplegics than in the paraplegics.

Although BMI is a poor surrogate measurement for body fat, plasma or serum leptin levels correlate with the BMI in the general population as well as in subjects with SCI[17,19]. This study confirmed this finding. Bauman et al measured body fat mass of a group of male subjects with SCI by dual-energy X-ray absorptionmetry and found that plasma leptin levels correlate with the percent of the total body fat mass, better than with the BMI, in a nonlinear way[17]. In this study, a nonlinear relationship was found between the BMI and serum leptin levels in subjects with SCI. A peculiar J curve was noted at the lowest BMI. This suggested that in addition to the fat mass there are other factors involved in the regulation of the serum leptin level. It is interesting to note that at a low BMI (< 16 kg/m^2) there are inappropriate high serum leptin levels in subjects with SCI. This "J" phenomenon is only seen in subjects with SCI and not in the normal controls. Although the BMI of the normal controls do not reach such a low level, the linear correlation between the BMI and the serum leptin level still persisted in subjects with anorexia nervosa whose BMI are as low as 13 kg/m^2 [20]. Since the number of subjects in the SCI group with a low BMI is small, the "J" phenomenon needs to be

reconfirmed.

Overexpression of ob gene mRNA and oversecretion of leptin in the adipose tissue of obese subjects may explain the exponential relationship between the serum leptin level and the BMI[19]. However, elevated serum leptin levels in obesity also suggest leptin resistance in obese person. Hormonal factors and several cytokines were shown to alter serum leptin level[21-26]. Thus, prolonged insulin infusions or supraphysiologic insulin levels caused a marked increase in circulating leptin levels[21,22]; hyperadrenergic state decreased serum leptin levels[23]; exogenously administered glucocorticoids increased serum leptin levels[24]. Several cytokines such as tumor necrosis factor - α, interleukin-1 and interleukin-6, also altered leptin mRNA expression and circulating levels[25,26]. However, Bauman et al showed plasma leptin levels did not change after a 3-hour oral glucose tolerance test in subjects with SCI[17]. Recently, circulating leptin levels are found to be inversely related to pituitary-adrenal function in humans[5,6] and leptin directly inhibits cortisol synthesis by adrenal cells[27]. Thus, leptin and cortisol interact in a negative feedback loop. In this study, there was no correlation between cortisol and leptin levels in normal controls. The cause of the discrepancy is unknown. It may be that one blood sample can not stand for the status of leptin and cortisol as both hormone levels are pulsatile. Yet, it showed a negative correlation between serum cortisol and leptin levels in subjects with SCI. This negative correlation remain significant ($p = 0.0260$) after adjustment for the BMI effect by multiple regression analysis. Recently, a impaired adrenal reserve was reported in subjects with SCI[12,28]. Whether the elevated serum leptin levels in SCI contribute to the low cortisol level needs further investigation. Although thyroid hormone regulates the expression of leptin mRNA and secretion of leptin by adipocyte in vitro[29], leptin concentrations do not change in response to hyperthyroidism[30]; instead, they decrease in hypothyroidism[30]. In this study, the serum T_4 level is negatively correlated with the serum leptin level, but this relationship became insignificant after adjustment of the BMI effect. SCI represents a chronic euthyroid sickness with possible recurrent episodes of urinary tract infection. Furthermore, glucocorticoid inhibit cytokines synthesis[31] and impaired adrenal reserve was noted in subjects with SCI[13,28]. So SCI may be associated with the elevation of various cytokines by reduced serum cortisol and/or concurrent infections. Elevated cytokines may also contribute to the elevation of serum leptin. Currently, there is no information regarding serum cytokines levels in subjects with SCI.

SCI result in muscle paralysis and atrophy. Inactivity and reduced resting energy expenditure[32] leads to a relative and absolute increase of fat mass in subjects with SCI[14-18]. Reduced sympathetic activity is also noted in subjects with SCI[33,34]. Local sympathetic denervation of white adipose tissue in rats induces preadipocyte proliferation[35]. Furthermore, adrenergic stimulation down-regulate the leptin expression and secretion by adipocyte[23]. Sympathetic denervation of adrenal gland causes reduced adrenal corticosteroid response to stress and stimuli[36]. Impaired HPA axis was noted in a high proportion of the subjects with SCI[12,28]. Previous hormonal studies suggest there are central neurotransmitter alterations after chronic SCI[11-13]. It is possible that central neurotransmitter alterations also plays a role in the elevation of the serum leptin level in subjects with SCI.

四、計畫成果自評

In summary, a linear correlation between the serum leptin and the BMI was demonstrated in subjects with SCI and normal controls. A stronger polynomial correlation between serum leptin and BMI was shown in subjects with SCI. A "J" phenomenon was noted at the lowest BMI. A negative correlation between serum leptin and serum cortisol levels was found in subjects with SCI. Sympathetic denervation and alterations of central neurotransmitter tone may contribute to the elevation of serum leptin and the depression of serum cortisol in SCI.

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