Hormones, aging and cognition in Asian men

Short Title: Endocrine factors, memory and perception capacities and aging in Asian men

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ABSTRACT

Background: This cross-sectional study examined the associations of hormones and age with short-term memory and perceptual capacity in 472 healthy Asian men. **Methods:** The symbol digit and digit span tests from the Swedish Performance Evaluation System were used to assess perceptual capacity and memory. Linear regression analyses with the stepwise method were carried out with the SPSS 21.0 package. **Results:** Age was associated with lower dehydorepiandrosterone sulphate (DHEAS), insulin growth factor-1 (IGF-1), thyroxine (T4), testosterone (T), bioavailable T (BioT), and error rate (Err) but higher glucose (GLU), sex hormone binding globulin (SHBG), estradiol (E2) and retention time (RT). High GLU was associated with higher error rate, longer RT of the perceptual capacity domain and shorter DSpan of the short memory domain. Higher BP3 was associated with longer DSpan. High Cor was associated with higher Err, while high DHEAS was associated with shorter RT. All other hormones from the adrenal, somatotrophic and gonadal were not significantly associated with cognition. **Conclusion:** The findings suggest 1) a role for tighter control of blood glucose levels in cognitive decline with aging in both healthy and diabetic people, 2) different hormones may be related to different parameters of cognition and "cognition" is not a unitary phenomenon and 3) further investigation of the potential for exogenous DHEAS to slow cognitive decline in aging, especially as it relates to reaction time. (220 words)

Key words: Hormones, short-term memory, perceptual capacity, cognition, aging, Asian men

INTRODUCTION

Aging is associated with changes in the functionality of various health compartments, including that of metabolic, cardiovascular, cognitive and endocrine compartments [1-6]. In addition, the effects of aging occur in an inter-compartmental manner, where changes in one may affect others [7, 8]. Evidence is beginning to accumulate which suggests that age-related changes in endocrine activities may be related to cognitive decline in man [9]. However, a direct relationship between cognitive and endocrine changes has been difficult to prove. The difficulty may, in part, be due to the complexity of human cognition and the lack of accurate and reliable tools to measure the functional capacity of the different cognitive domains. Furthermore, it has been shown that cognition is affected by many factors including lifestyle, biochemical, social, environmental, genetic and hormonal factors [8, 10, 11]. Amidst the many confounding factors, the challenge to tease out the individual factors having independent association with cognition is considerable. It is unclear whether age-related changes in the various endocrine axes are associated with cognition.

The gonadal, adrenal, somatotrophic and thyroid axes may have roles in the establishment and modulation of human behavior and cognition [9]. However, the associations of these endocrine axes with cognition and their potential effects on the aging brain remain uncertain [9]. Androgens were noted to be associated with visuospatial functions in elderly men on testosterone therapy and in men with Alzheimer' disease (AD) or mild cognitive impairment (MCI) [12-15], but others have shown otherwise [16-18]. The conflicting results could be related to the ages of the men, the endogenous levels of testosterone present and the cognitive function tests employed.

The adrenals secrete large amounts of DHEA and DHEAS (DHEA/S) and cortisol. With aging,

there is a progressive and continuous decline of DHEA/S levels [19]. On the other hand, cortisol levels show a slight parallel linear increase with aging or remain largely unchanged [19]. Several earlier studies did not show a link of DHEA/S with cognition [20, 21], but others did [22-25]. The available evidence does not currently support a clear role of DHEA/S in improving or maintaining memory and other cognitive domains in healthy older individuals, but it might be useful in older persons with MCI or in the context of a hormonal deficiency [26].

High levels of cortisol are associated with poorer memory and it seems to be associated with hippocampal function [27, 28]. However, it has also been shown that the decline in cognition with aging was not paralleled by changes in cortisol levels [29].

Somatotrophic hormones such as growth hormone (GH) and insulin-like growth factor-1 (IGF-1) may play an important role in brain function [30]. Growth hormone and IGF-1 decline with age and the declines are associated with poorer cognitive functions [31, 32]. The link between lower levels of IGF-1 and poorer cognitive function was derived from both cross-sectional and intervention studies with GHRH therapy [33-35]. Whether endogenous levels of somatotrophic hormones have any modulating effects on cognition remains unclear.

Clear evidence does exist on the role of thyroid hormones in adult brain function [36, 37]. Evidence of the association of thyroid hormones with cognition was derived from studies of patients with either hypothyroidism or hyperthyroidism [38, 39].

SUBJECTS, MATERIALS AND METHODS

Subjects

This study involved analyses of data collected from a group of 472 men. Details of recruitment of the subjects have been reported in several earlier publications [7, 8]. Subjects were healthy men, aged between 29y to 72y living in the community.

Methodologies

Each subject answered a self-administered and investigator-guided questionnaire. Questions asked included medical, dietary, social, sex, and family histories and other histories regarding consumption of hormones, supplements and medication, types of beverages, smoking and alcohol consumption.

To improve our understanding of the associations between hormones, aging and cognition, we have concurrently measured hormone levels, lifestyle factors and cognitive function in healthy men. This has enabled the evaluation of the individual hormones' association with cognition with adjustment for various confounding factors.

Cognitive function tests

The Swedish Performance Evaluation System (SPES) was developed over the last 40 years [40]. Two tests from the SPES, the Symbol Digit for perceptual capacity and Digit Span for short-term memory were used in the study.

Symbol Digit – The Symbol Digit is a test of perceptual capacity which includes matching, memory and the speed of processing. In one row, a key to this coding task is given by the pairing of symbols with randomly arranged digits, 1 to 9. The task is to key in as fast as possible the digits corresponding to the symbols presented in random order in a second row. Each set consists of nine pairs of randomly arranged symbols and digits, and a total of 10 sets are presented. Performance is evaluated as the mean reaction time (msec) (RT) and the number

of errors (Err) for the last 54 pairs of the test. Symbol Digit tests the individual's ability to interpret and correctly match what he sees as well as the speed of his perceptual processing. It also involves hand-eye coordination. The two components of this test are reaction time (RT) and the number of errors (Err) [40].

Digit Span – The Digit Span is a test of short-term memory capacity. In this test, a series of digits is presented on the screen. The digits are presented one at a time with a 1-second presentation time, and the task is to reproduce the series on the keyboard. Depending on the answer, the length of the following series is either increased or decreased. The test starts with a series of three digits and it is terminated after six incorrect answers. Performance is evaluated as the maximum string of numbers (DSpan) that the subject could remember successfully. A longer DSpan indicates a better short term visual memory [40].

The digit symbol and digit span are computer-based tests. All participants underwent a familiarization trial test before the actual scorings were recorded.

Exercise scores (MET-min)

Exercise may interact with both hormone levels and with cognition [6, 8]. The type, duration and frequency/week of exercise for each participant were collated from data from the self-administered and investigator-guided questionnaire. The intensity of the physical exercise was scored using the Metabolic Equivalent of Task (MET) for each exercise type. The scoring took into account the duration of each exercise episode and the frequency of the exercise per week to derive an exercise score. In accordance with the guidelines for Americans [41], the MET cut-off values were as follows: light intensity (<3 MET), moderate intensity (3–6 MET) and high intensity (>6 MET). The total exercise score per week was expressed as metabolic equivalent-min (MET-min). The manner of calculating this score has been reported earlier [8, 42].

Measurements of hormones

Measurements for T, E2, DHEAS, Cortisol and SHBG

A 12 h fasting blood sample was collected from each participant and serum separated and stored at -80^{o}C. Serum testosterone (T) and estradiol (E2) concentrations were measured using reagents and methods recommended by the World Health Organization Matched Reagent Program [43] with modification to the scintillation proximity methods established in-house [44]. Dehydroepiandrosterone sulphate (DHEAS) and sex hormone binding globulin (SHBG) and cortisol (Cor) were measured by established radioimmunoassay methods reported earlier [45]. The intra- and inter-assay coefficients of variation were less than 10% over the effective concentration ranges for T, DHEAS, and Cor and less than 15% for E2 and SHBG.

Measurements for IGF-1, BP3, INS, TSH, T4, T3 and GLU

Serum concentrations of insulin-like growth factor-1 (IGF-I) and insulin like growth factor binding protein-3 (BP3) were measured using immunoradiometric assay kits (Diagnostic Systems Laboratories, Inc., Webster, TX) as reported earlier [46, 47]. The CV for duplication was <10%. The ranges for inter-batch-assay CV were 3.6–4.5% for serum IGF-I and 6–9% for serum BP3. Serum concentrations of insulin (INS), thyroid stimulating hormone (TSH), T4 and triiodothyronine (T3) were measured in-house using the Axsym platform from Abbott. Glucose levels were measured using the hexokinase method on the in-house Axsym platform.

Method of calculation of Bioavailable T (BioT)

BioT was calculated using the computer formula of Vermeulen, which is available on the ISSAM website (www.issam.ch). Total T was computed as ng/dL, and SHBG as nmol/L. Albumin level was assumed to be 44. Hence, BioT was expressed an ng/dL [48].

Statistical analysis

Statistical analyses were performed using SPSS for windows version 21.0 (Armonk, NY). Multilinear regression with the stepwise method was used for the various hormonal factors with the three parameters of the two cognitive domains studied.

RESULTS

Table 1 shows the correlation between age and hormones from the gonadal, adrenal, somatotrophic (including GLU) and the thyroid axes as well as the three parameters of cognition studied. Independent of other hormones, age was associated with decline in DHEAS, IGF-1, T4, T, and BioT, but increase in GLU, SHBG, E2 and RT. As was reported earlier [43], in this sample, the older Singaporean men were exercising more intensely than younger men (Table 1). Other hormones did not show any age-related changes (Table 1).

Table 2 shows the linear regression analyses, using the stepwise method, of hormones from the gonadal, adrenal and somatotrophic axes, age and exercise score with the three cognitive parameters of Err, RT and DSpan. Glucose is an important factor in the somatotrophic axis and was included in the analyses. The circulating level of glucose was significantly associated with all three parameters of the two cognitive domains studied. High GLU was associated with higher error rate, longer RT of the perceptual capacity domain and shorter DSpan of the short memory domain (Table 2). The IGF-binding protein-3 (BP3), the other component of the somatotrophic axis, was significantly associated with the memory domain; higher BP3 was associated with longer DSpan (Table 2). As was reported in an earlier study, age was positively associated and MET-min was negatively associated, with RT of the perceptual domain (Table 2). Two hormones from the adrenal axis, Cor and DHEAS, were significantly associated with cognitive functions. High Cor was associated with higher error rate (Err), while high DHEA/S was associated with shorter RT (Table 2). All other hormones from the adrenal, somatotrophic and gonadal axes were not significantly associated with the three parameters of the two cognitive domains (Table 2).

DISCUSSION

The role of the neuroendocrine system, and in particular, the role of hormones in cognition has been established mainly through models of endocrine dysfunction such as congenital adrenal hyperplasia, menopause syndrome, hypogonadism, diabetes and hormone replacement therapy [9]. It is however, unclear to what degree, if any, age-related changes in endogenous hormone levels are associated with decline in cognition in aging men. The present cross-sectional study evaluated whether age-related differences in endogenous hormone levels are associated with cognitive functioning in healthy community living men.

Aging has varying effects on healthy individuals, with some people exhibiting extensive alteration in physiological functions including cognition but others little or none [49-52]. As we have reported earlier, age and a lifestyle habit of physical exercise were significantly associated with the perceptual capacity [6]. Hence, in the present study, all correlational analyses of hormone levels with cognitive functions were adjusted for age and exercise intensity. If this is not done, the relationships of individual endogenous hormone levels with cognition might be confounded.

The regression analyses showed that endogenous levels of GLU were significantly associated with all three parameters of the perceptual and short-term memory cognitive domains. Higher circulating levels of glucose were associated with poorer perceptual capacity, with higher error rate and longer retention time. At the same time, higher levels of glucose were associated with poorer short term visual memory. In the present study, none of the participants was diabetic or on medication for diabetes and their glucose levels were not in the pathological range. Therefore, the negative correlation of the glucose levels with the three parameters of cognition suggests that circulating levels of glucose per se may have a modulating effect on short term

memory and perceptual capacity. This finding implies that tighter control of blood glucose levels in diabetics and healthy men may modulate a high GLU-associated decline in cognition and should be investigated in future studies.

It has been suggested that prenatal exposure to androgens strongly influences the cognitive pattern in adulthood [53]. Androgens (either directly or through conversion to estrogens) may be associated with visuospatial cognitive ability. This may be observed in patients with androgen excess, as in cases of congenital adrenal hyperplasia [54], and androgen insensitivity [55]. However, the association of androgens with cognition in studies of cross-sex hormone therapy in transsexuals and hormone replacement in hypogonadal men were equivocal [56, 57]. In addition, the relation between baseline endogenous circulating androgens and spatial ability remains unclear [9]. We have shown that circulating levels of testosterone, BioT, SHBG and estrogen were not significantly associated with any of the three parameters of cognition, in line with observations of several earlier studies [27, 58, 59] but in contrast to some other studies [60, 61]. The observation that the age-associated decline in androgens and increase in estradiol were not associated with cognition implies that circulating endogenous levels of sex hormones may not have a direct effect on cognition in men. The results imply that none of the gonadal factors has a modulating effect on cognition.

Cortisol and DHEA/S have been shown to be associated with human cognition [22, 26, 28]. Age was associated with a linear decrease in DHEA/S levels, but not with circulating levels of cortisol. We have shown that higher cortisol levels were associated with higher error rate, and higher levels of DHEAS were associated with lower RT in the perceptual capacity domain. The results suggest that these two hormones from the adrenal gland may have a role in the perceptual capacity domain of human cognition. We have shown that after adjusting for age,

exercise intensity and other hormone levels, DHEA/S in a group of normal men aged 29y to 72y was independently and significantly associated with cognition. By contrast, the Massachusetts Male Aging Study did not show any significant association between endogenous levels of DHEA/S and working memory, speed/attention and spatial ability in older men [27]. It has been suggested that a decline in DHEA/Cortisol ratio may underlie some of the cognitive decline associated with aging as DHEAS can attenuate the deleterious effects of cortisol [62, 63]. However, this suggestion was not borne out in the present study. We did not show any significant association of DHEAS/Cor ratio with any of the three parameters of cognition evaluated.

While cortisol shows a relative steady level of secretion throughout aging, DHEAS synthesis peaks in young adulthood and declines with age and by up to 80% in old age [8, 64]. It has been suggested that the effect of DHEAS is mediated indirectly through conversion to androgen or estradiol [65]. However, as shown in the present study, androgens and E2 in the same group of men were not significantly associated with the two cognitive domains. This observation may imply a direct role of DHEAS per se in modulating the perceptual capacity. A direct role of DHEAS in cognition is supported by our earlier observation that DHEAS affects sexual motivation in men, whereas androgens and estrogens do not [66].

Age-related decline in cognition and Alzheimer's disease have been associated with high cortisol levels in some studies [28, 67, 68], but not in others [29, 69]. The reasons may relate to artefacts due to the biological media in which cortisol was measure and to the measures of cognitive functions used [28, 29, 68-70]. In the present study, we noted a direct correlation of circulating cortisol levels with the error rate in the perceptual capacity in healthy men. This observation is in contrast to that of Gaysina et al [27], who did not show a significant

relationship of morning cortisol to midlife cognition.

Somatotrophic hormones play an important role in brain function [31]. Age-related decline in growth hormone (GH) and IGF1 in men concurrent with decline in cognition have been well established [31, 32, 71]. However, whether endogenous levels of somatotrophic hormones have modulating roles on real time cognitive functions in healthy men is less clear. As with circulating insulin, IGF-1 and the IGF/BP3 ratio were not significantly association with any of the three parameters of cognition evaluated. However, endogenous circulating levels of BP3 were positively associated with short-term memory. These observations were in contrast to those of some earlier studies [72]. The result implied that BP3 per se may have a direct role in modulating the short-term memory domain in human cognition.

Clear evidence exists on the role of thyroid hormones in adult brain function [36, 37]. Studies of patients with hypothyroidism and hyperthyroidism have shown that thyroid hormones are associated with cognition [38, 39]. However, in the present study none of the thyroid hormones was significantly associated with perceptual and short-term memory cognitive domains. This suggests that endogenous levels of T4, T3 and TSH may not have a modulating role in the short-term memory and perceptual capacity domains of human cognition in healthy men.

We have shown that circulating levels of GLU, DHEA/S, Cor, and BP3 were significantly associated with at least one of the parameters of the perceptual and short-term memory domains of human cognition.

A limitation of this study is that it is a cross-sectional study; hence no causal effect is attributable to the observed associations. Only two cognitive domains, the perceptual and

memory domains were studied, hence cross comparisons with studies with other domains of cognitions could not be made. On the other hand, a positive contribution of the present study is the involvement of a relatively wide age range (29 years to 72 years) of Asian men who were healthy with no history of any major illnesses that might mar the actual association of endocrine factors and age with cognition. In addition, a range of lifestyle factors was able to be controlled for.

The findings suggest three conclusions and/or hypotheses for further investigation:

1. A role for tighter control of blood glucose levels in cognitive decline with aging in both healthy and diabetic people.
2. Different hormones may be related to different parameters of cognition and "cognition" (thus cognitive decline) is not a unitary phenomenon.
3. The potential for exogenous DHEA/S to slow cognitive decline in aging, especially as it relates to reaction time.

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DECLARATION OF INTEREST

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Table 1: Linear regression analyses of age with endocrine factors and cognitive functions using the stepwise method of analyses.

Age vs	**Beta**	**p-value**
DHEAS	**-0.198**	**<0.001**
SHBG	**0.225**	**<0.001**
T4	**-0.159**	**<0.001**
Glu	**0.094**	**0.029**
METmin	**0.158**	**<0.001**
T	**-0.164**	**<0.001**
BioT	**-0.170**	**<0.001**
E2	**0.121**	**0.006**
IGF1	**-0.095**	**0.028**
RT	**0.179**	**<0.001**
Err	-0.081	NS
DSpan	-0.027	NS
BP3	-0.018	NS
IgfBpR	0.009	NS
INS	-0.007	NS
Cor	0.046	NS
TSH	-0.061	NS
T3	-0.091	NS

Table 2: Linear regression analyses separately of Err, RT and DSpan with various endocrine factors using the stepwise method of analysis.

Err	**Beta**	**p-value**	**RT**	**Beta**	**p-value**	**DSpan**	**Beta**	**p-value**
GLU	**0.173**	**<0.001**	**Age**	**0.241**	**<0.001**	**GLU**	**-0.111**	**0.021**
Cor	**0.095**	**0.049**	**METmin**	**-0.139**	**0.003**	**BP3**	**0.110**	**0.022**
Age	-0.024	NS	**GLU**	**0.100**	**0.032**	Age	-0.050	NS
METmin	-0.085	NS	**DHEAS**	**-0.121**	**0.014**	METmin	0.039	NS
T	-0.010	NS	T	-0.006	NS	T	0.052	NS
SHBG	-0.015	NS	SHBG	0.025	NS	SHBG	0.046	NS
BioT	0.001	NS	BioT	-0.017	NS	BioT	0.044	NS
IGF1	0.052	NS	IGF1	-0.030	NS	IGF1	0.036	NS
BP3	-0.049	NS	BP3	-0.040	NS	IGF/BP	0.028	NS
IGF/BP	0.093	NS	IGF/BP	-0.001	NS	INS	0.008	NS
INS	-0.003	NS	INS	-0.030	NS	Cor	0.004	NS
E2	0.025	NS	Cor	0.025	NS	E2	-0.021	NS
DHEAS	0.004	NS	E2	0.055	NS	DHEAS	0.006	NS
TSH	-0.024	NS	TSH	0.019	NS	TSH	-0.035	NS
T4	-0.027	NS	T4	0.021	NS	T4	-0.037	NS
T3	-0.012	NS	T3	0.001	NS	T3	0.008	NS