Testosterone levels and discounting delayed monetary gains and losses in male humans

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Abstract

OBJECTIVES: Although impulsivity has been associated with androgens (e.g., testosterone), little is known regarding the relationship between testosterone levels and impulsivity in intertemporal choice (delay discounting). This study was aimed to examine the relationship between delay discounting of gains and losses and testosterone levels, which is of interest in neuroendocrinology and neuroeconomics.

METHODS: We assessed degrees to which delayed monetary gains and losses were discounted (hyperbolic discounting rate) in healty male students (age: 22.4±2.67). Participants' salivary testosterone levels were also assessed by utilizing liquid chromatography/mass spectroscopy (LC/MS) method.

RESULTS: Non-linear curve fitting analysis showed an inverted-U relationship between delay discounting of gains and salivary testosterone levels; while no relationship between salivary testosterone levels and delay discounting of losses was observed.

CONCLUSIONS: The results indicate that (i) testosterone may enhance delay discounting rate of gains in non-impulsive subjects, (ii) testosterone may have an opposite (reducing) effect on delay discounting rate of gains in impulsive subjects, and (iii) testosterone is unrelated to subject's sensitivity to future bad outcomes. Implications for evaluating the effects of testosterone treatment and anti-androgenic therapy on impulsive behavior often observed in psychiatrics (e.g., pathological gambling, credit card debt, substance misuse, and needle-sharing) are discussed.

ORIGINAL ARTICLE

1. INTRODUCTION

Impulsivity is a core deficit in neuropsychiatric illnesses such as drug-dependence, attention-deficit-hyperactivity disorders (ADHD), and psychopathy [1,25]. As such, neuropsychological functioning associated with impulsivity has attracted much attention [1,10]. Several previous investigations into the role of testosterone in impulsive/aggressive/risky behavior reported that (i) elevated testosterone levels are associated with impulsivity and aggression (e.g., criminal behavior [14]) and (ii) serotonergic activity in the central nervous system has a pivotal role in modulatory influences of testosterone on impulsivity and aggression [6]). However, to date, no

study on testosterone-impulsivity relationships has operationalized impulsive behavior in a manner which can sensitively detect individual differences. More specifically, although previous studies have reported a testosterone administration induced impulsive/risky decision-making on the IOWA gambling task [23], little is known about the relationship between testosterone levels and impulsivity in intertemporal choice (delay discounting). In this study, we operationalized risky/impulsive behavior as a marked devaluation of delayed monetary gains and losses leading to a preference of small immediate rewards over large delayed ones; and aversion to small immediate losses over large delayed ones (delay discounting of monetary gains and losses), following a standard behavioral paradigm in neurobiochemical and neuroeconomic studies of impulsivity [1,7,8,9,12,15]. Notably, impulsive psychiatrics (e.g., drug addicts, pathological gambles, and ADHDs) are reported to have stronger delay-discounting tendency than healthy controls [1,8,12,15]

It is known that monoamines (e.g., dopamine and serotonin) in the central nervous system and drug dependence-induced neuroadaptaion in dopaminergic reward circuitry modulate delay discounting behavior [25]. We have also previously reported that severity of nicotine addiction is positively associated with the degree to which smokers discount delayed monetary gains, but not with monetary losses [12]. Furthermore, because gains are more rapidly discounted than losses possibly due to involvement of distinct mediating neural processes between delayed gains and losses (i.e., sign effect) [1,2,19], it is important to examine delay discounting of both gains and losses.

Previous studies reported a gender difference in degrees to which delayed gains are discounted (i.e., discounting rates, explained below); i.e., women are less impulsive than men in intertemporal choice [7]. We have further found an association between concentrations of a stress hormone (cortisol) and discounting [17]. Moreover, it has been reported that an exposure to androgens alters the activity of dopaminergic neurons in the mesocorticolimbic reward system [20], and male discounting rate of monetary gains is dramatically increased by an exposure to photographs of attractive women [24]. Together, it is supposable that sex hormones (e.g., testosterone) are associated with discounting behavior in a manner yet to be investigated. Moreover, because (i) low monoamine activities are strongly associated with large degrees of discounting, as stated above (i.e., subjects with strong impulsivity in intertemporal choice may have a reduced serotonergic/dopaminergic activity), and (ii) the modulatory role of testosterone in impulsivity/aggression is under the influence of monoamine (e.g., serotonin) activity in the brain [6], it might be expected that relationships between testosterone levels and discounting may be non-linear ones, rather than a simple linear one; namely, the sign (i.e., positive or negative) of relationships between testosterone and discounting rate might possibly differ in subjects with high and low impulsivity in intertemporal choice. With respect to this point, although testosterone administration induces impulsive/risky behavior in a gambling task [23], one study has reported that there is no significant difference in testosterone levels between pathological gamblers and normal controls [3]. This discrepancy might possibly be resolved if the relationship between impulsivity and testosterone levels is not a simple linear one. It is also noteworthy that the relationship between spatial ability and testosterone levels has been observed to be a non-linear, invert U-shaped (quadratic) relation, rather than a simple linear one [5]. In this study we therefore examined non-linear relationships between salivary testosterone levels and delay discounting rates of gains and losses in healthy male students, by utilizing well-established Kirby's MCQ (monetary choice questionnaire) for the assessment of subjects' discounting rates [8].

2. METHOD

2.1. Participants and saliva collection

A total of 75 healthy male students (age: 22.4±2.67) participated in the present study. It should be noticed that, to avoid influences of chronic nicotine-induced neuroadaptation on discounting behavior [12,15], only non-smokers were included in the study. Further, subjects with physical or psychiatric illnesses were excluded. Each participant collected two saliva samples in the mornings (7:00–8:30). The participants were asked to refrain from sexual intercourse and the consumption of alcohol beginning from the night before the samples were collected and, as far as possible, to obtain sufficient sleep. They were also instructed to maintain an interval of 6 h after brushing their teeth, at least 1 h after eating or drinking any fluid other than water, and 30 min after any strenuous exercise while collecting the samples of saliva. A stick of sugarless chewing gum (Recaldent mild mint flavor) was used to stimulate saliva production. Each participant stored his saliva samples at –20 °C, and using coolant bags, brought these samples to the experimenters within two days of collecting them. The samples were stored in the laboratory of the Teikoku Hormone Mfg. Co., Ltd., and within a week after the collection, they were processed for measurement as will be described later. The participants also answered Kirby's questionnaire (explained below [8]) for the assessment of their discounting rates of delayed gains and losses, and received a nominal amount of money (1,000 yen). This study was approved by the ethical committee on the use of human subjects at the Graduate School of Arts and Sciences, the University of Tokyo.

2.2. Materials

2.2.1. Kirby's MCQ (monetary choice questionnaire)

Delay discounting of gains and losses is well described by the following hyperbolic discounting function [1,8,15]:

$$V(D)=1/1+kD \qquad \text{(equation 1)}$$

where V(D) is a subjective value of delayed rewards at delay time D, and k (a discount rate) is a free parameter indicating subject's impulsivity in intertemporal choice (larger k values correspond to more rapid/steeper discounting). In order to assess subject's discount rate k, as defined in equation 1, Kirby's MCQ [8] was used. Kirby's MCQ consists of 27 questions relating to a choice between smaller immediate rewards and larger but delayed rewards (e.g. "Would you prefer 54 dollars today or 55 dollars in 117 days?"). In the present study, we also used a loss-version of Kirby's MCQ, in which all questions related to a choice concerning losing/paying money (e.g. "Would you prefer paying 54 dollars today or paying 55 dollars in 117 days?"). According to the standard analysis procedure of MCQ, established by Kirby and colleagues [8], we calculated subjects' discounting rates (i.e. ks) of three different sizes (small, medium, and large) of monetary gains and losses. A total of six discount rates (i.e., small gain, medium gain, large gain, and small loss, medium loss, and large loss) were obtained for each subject. Geometric-mean discounting rates for different sizes were calculated, following Kirby's procedure [8]. We then examined relationships between mean discounting rates of gains and losses, and salivary testosterone levels. It should be noted that in our Kirby MCQ form, all gains and losses were expressed in terms of Japanese yen, with an exchange rate of one dollar to 100 yen. Because the distribution of the discount rate k is known to be skewed, we used logged k (Ln(k), a natural log) in the analysis between discounting rate and testosterone levels, according to a standard analytical procedure [8].

2.2.2. Salivary testosterone assay

For measuring the T levels, 1 mL of saliva from each sample was used. All procedures for salivary testosterone assay by utilizing LC/MS method were conducted at Teikoku hormone medical (Japan), which has significant experiences in various hormonal assays [17,18]. Staff at the company did not know the nature of the present behavioral assessment.

An analytical curve was created from 5, 10, 20, 65, 125, 500, and 1000 pg standard T (Sigma-Aldrich, Tokyo, Japan) in 50 μL methanol. These standard analytes were processed in the same manner as the other analytes. The internal standard was 1 ng T-d_3 (Sigma-Aldrich) in 50 μL methanol, and it was added to every analyte. The standard T samples were diluted with 1 mL purified water.

Two hundred microliters of a 2% dichloromethane solution of 2-Fluoro-N-methylpyridinium p-sulfonate (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan) and 30 μL of a 10% dichloromethane solution of triethylamine were added to the ether-extracted analytes and maintained at the ambient temperature for 1.5 h for derivatization [13]. The solvent was then removed by evaporation and the analytes were dissolved in a 25% aqueous solution of methanol (1 mL) and charged on a Bond Elute C18 cartridge (Varian, Palo Alto, CA, USA) conditioned with methanol and deionized water. The cartridge was successively rinsed with 1 mL deionized water, 3 mL ammonia water, 2 mL methanol, and a mixture of 0.01% aqueous solutions of formic acid and methanol (3 mL). The analyte was eluted with a mixture of 10% aqueous solutions of formic acid and acetonitrile (2.5 mL).

The analytes were measured with an electrospray mass spectrometer API4000™ (Applied Biosystems/MDS SCIEX, Tokyo, Japan) in the positive ion mode. This device monitored the *m/z* 380 to *m/z* 253 (T) and *m/z* 383 to *m/z* 256 (T-d_3) transitions. The ion spray voltage was set to 5000 V.

2.3. Data analysis and statistical procedure

Following Kirby's procedure, the averages of logged discounting rates of gains and losses were calculated as denoted above. According to a standard procedure in examination of testosterone-cognitive function relationships [5], we then conducted non-liner (quadratic) curve fitting analysis between average discounting rates of gains and losses, in order to examine relationships between testosterone levels and impulsivity in delay discounting of gains and losses, by utilizing a non-linear curve fitting library of R statistical language (i.e., "nls"). More specifically, the following quadratic equation:

$$y=ax^2+bx+c, \qquad \text{(equation 2)}$$

where y = testosterone level, x = logged discounting rate k in equation 1; additionally, a, b, and c are free parameters to be estimated, was employed for the non-linear curve fitting, after the confirmation of non-existence of a significant linear relationship by utilizing Pearson's product-moment correlation analysis. To examine whether gains are more steeply discounted than losses, we conducted Mann-Whitney's U-test. Data are expressed in terms of Mean ± SD. Significance level is set at 0.05 throughout.

3. RESULTS

3.1. Characteristics of salivary testosterone level and discounting rate

Subjects' salivary testosterone level was 97.25±24.2 pg/mL. This range of salivary testosterone levels is similar to values reported previously [16,21].

The average discounting rate (i.e., k in equation 1) of gains and losses were 0.023±0.038 and 0.0012±0.0039, respectively, which are similar to values reported in a previous study [8]. Discounting rates for losses were smaller than those for gains (p<0.001), consistent with a previous finding that losses are more slowly (less steeply) discounted than gains [12,19].

3.2. Relationship between discounting rate and testosterone level

Pearson's correlation analysis showed no significant linear correlation between the averaged discounting rates of gains and losses and salivary testosterone levels. Then we conducted non-linear (quadratic) curve fitting analysis between discounting rate and testosterone level. We observed a significant quadratic (invert U-shaped) relationship between discounting rate of gains and salivary testosterone level (Fig. 1); in contrast, there was no significant quadratic relation between discounting rate of losses and salivary testosterone levels (Fig. 2). It should be denoted that estimated

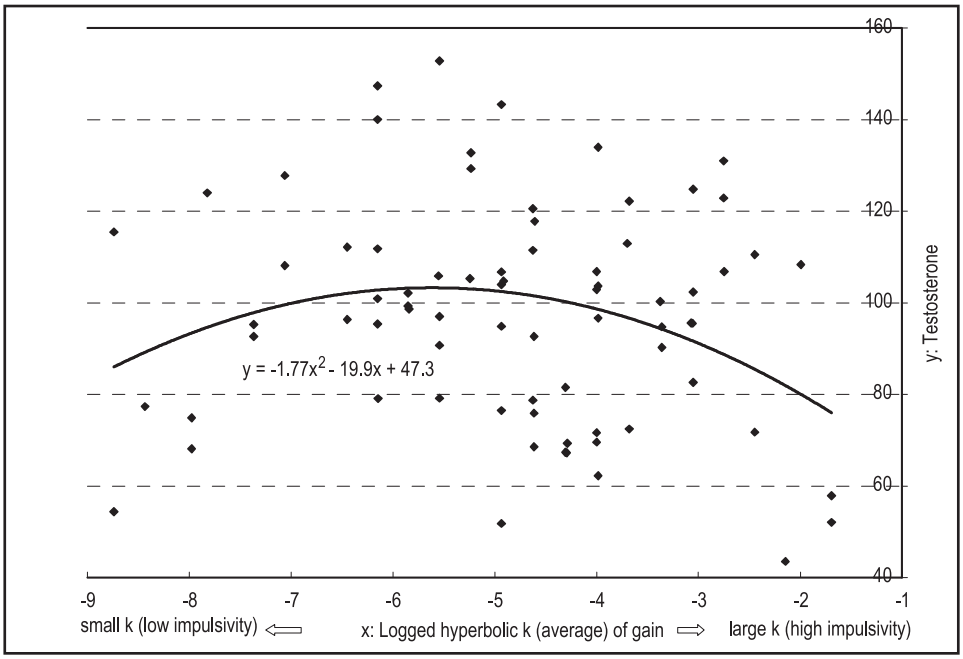

Fig. 1: Scatterplot of discounting rate of delayed gains and testosterone levels. Horizontal axis indicates logged hyperbolic discounting rate k of delayed gains, and vertical axis indicates testosterone levels [pg/mL]. A significant quadratic, inverted-U relation was observed (p<0.05, for all coefficients). Note that large k corresponds to steep discounting (i.e., impulsivity in intertemporal choice on gains)

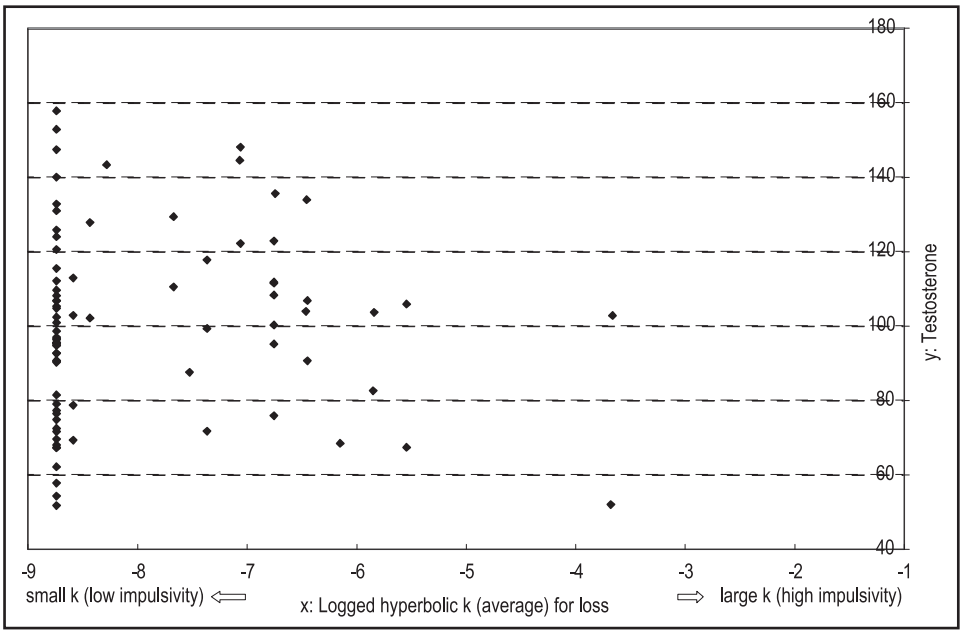

Fig. 2: Scatterplot of average discounting rate of delayed losses and testosterone levels. Horizontal axis indicates logged hyperbolic discounting rate k of delayed gains, and vertical axis indicates testosterone levels [pg/mL]. No significant relation was observed. Note that large k corresponds to steep discounting (i.e., impulsivity in intertemporal choice on losses)

values of the free parameters in equation 2 for delayed gains were a= –1.7739±0.7764, b= –19.9243±8.1541, and c=47.3447±20.1091 ($p<0.05$, for all coefficients) (Fig. 1). This indicates testosterone levels are positively associated with impulsive choice on delayed gains in subjects with low degrees of impulsivity (i.e., small k values), but negatively associated with impulsive choice in subjects with high degrees of impulsivity (i.e., large k values) (Fig. 1); in contrast, testosterone is unrelated to discounting rate of delayed losses (Fig.2).

4. DISCUSSION

4.1. Relationship between impulsive choice and testosterone

This study is the first to report the existence of an invert U-shaped relation between delay discounting rate of gains and testosterone. Our results suggest that testosterone has opposite effects on impulsivity in intertemporal choice on gains in subjects with high and low impulsivity. Specifically, in subjects originally with weak impulsivity (smaller k values), an increase in testosterone levels may result in more impulsive intertemporal choice on gains; on the contrary, it may reduce impulsivity in subjects initially with strong impulsivity (larger k values). Because (i) intertemporal choice is under strong modulation of monoaminergic (e.g., serotonergic and dopaminergic) activity in the brain [6,9], and (ii) testosterone modulates serotonergic activity-dependent impulsive behavior [6,20], it is possible that the observed inverted U-shaped relationship between discounting and testosterone reflects complex interactions between monoaminergic and androgenic modulation of intertemporal choice.

As mentioned earlier, previous findings on relationship between testosterone levels and impulsivity have been mixed: van Honk and colleague reported that increase in testosterone levels resulted in impulsive choice by healthy subjects in a gambling task [23]; on the contrary, Blanco and colleagues' study found no significant difference in testosterone levels between normal controls and impulsive pathological gamblers, known to have large delay-discounting rates [3,4]. Our present observation of an inverted U-shape relashionship may explain the discrepancy. Namely, impulsive psychiatrics (e.g., pathological gamblers) may have a lower testosterone levels, compared to impulsive but still normal healthy controls (note that testosterone is negatively associated with impulsive choice of subjects with strong impulsivity, Fig 1). Consistent with this account, a recent study actually reported that impulsive adolescent males' aggressive/delinquent behavior was reduced, rather than increased, when their testosterone levels were dramatically increased [22]. Nevertheless, our results imply that an increase in testosterone may enhance impulsivity of originally less impulsive subjects, in line with positive correlation between testosterone and aggression/impulsivity, especially in normal healthy women (note that women are less impulsive than men [7]) [2,23]. Together, it can be proposed that opposite manipulations of testosterone levels should be conducted for subjects with high and low impulsivity, to enhance their patience in intertemporal choice on rewards.

Another new finding of the present study is that discounting rate of delayed losses was not significantly related to testosterone levels in linear or non-linear (quadratic) manners. This indicates that when impulsive psychiatrics' problematic behavior is due to a reduced sensitivity to future/delayed bad consequences [1](e.g., health loss due to long-term substance misuse, possible HIV infection due to needle-sharing by substance misusers, and credit card debt of addictive gamblers) manipulation (either administration or reduction) of testosterone levels may be ineffective. This point should further be examined.

4.2. Limitation and future directions

Although we excluded smokers in order to control drug (i.e., nicotine) addiction-induced neuroadaptation predominantly in dopaminergic systems, we did not assess or manipulate activities of serotonergic systems. As noted above, serotonergic systems are known to strongly modulate intertemporal choice [9]. Therefore, manipulation or assessment of serotonergic activity in combination with testosterone assessment would be preferable in future studies. As noted, there is a sex difference in discounting behavior [7]. We employed only male subjects in the present study. How sex hormones are involved in female discounting behavior should also be examined in future studies. Additionally, because our present data reveal only correlational findings, future studies should preferably examine the effect of testosterone manipulation (administration of testosterone and/or pharmacological blockade of androgen receptors) on discounting behavior, in order to further elucidate androgenic modulation of impulsive behavior.

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