Neuroendocrine effects of citalopram, a selective serotonine re-uptake inhibitor, during life span in humans

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Neuroendocrine effects of citalopram, a selective serotonin re-uptake inhibitor, during lifespan in humans

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ABSTRACT. ***Objective:*** **Serotonergic system contributes to the regulation of hypothalamus-pituitary-adrenal axis. In humans, serotonergic agonists increase PRL, ACTH, and cortisol, while serotonin (5HT) influence on GH is controversial. Central 5HT activity and neuroendocrine function change during lifespan.** ***Design:*** **To clarify the neuroendocrine response to 5HT across lifespan, we assessed ACTH, cortisol, DHEA, PRL, and GH responses to citalopram (CT) in young adults (YA) (no.=12, 29.2±1.7 yr mean±SEM), middle aged (MA) (no.=12, 54.3±0.9 yr), and elderly (ES) (no.=12, 69.3±0.9 yr) males. All the subjects received placebo (saline iv over 120 min) or CT (20 mg iv over 120 min). Blood samples were taken every 15 min up to 240 min.** ***Results:*** **During placebo, ACTH, cortisol, GH, and PRL were similar in all groups while DHEA showed an age-dependent reduction from middle age ($p<0.001$). During CT, ACTH, and cortisol were higher than during placebo in YA ($p<0.05$) and even more in MA ($p<0.01$ *vs* placebo, $p<0.05$ *vs* YA); in ES, the increase of both ACTH and cortisol ($p<0.05$ *vs* placebo) was lower than in MA ($p<0.05$) and higher than in YA ($p<0.05$ for cortisol only). No changes were observed for DHEA, GH, and PRL in any group.** ***Conclusions:*** **Corticotrope response to CT is age-dependent in normal men, being amplified starting from middle age, suggesting precocious changes in the serotonergic neuroendocrine control during lifespan. CT is a useful tool to evaluate the age-dependent serotonergic function in humans.**
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INTRODUCTION

Serotonergic system is known to play a central role in the regulation of neurondocrine activity in animals and humans (1, 2). There is evidence that it is involved in the mediation of the hippocampal feedback regulation of the hypothalamus-pituitary-adrenal (HPA) axis. In fact, *in vitro* studies showed that serotonin (5HT) increases hippocampal mRNA expression of glucocorticoid receptors, in culture cells of rats, mice, and guinea pigs especially during certain periods of fetal life (3-5). In the hypothalamic paraventricular nucleus, direct synaptic connections between serotonergic neurons and CRH-secreting neurons have also been demonstrated (6) and, at this level, 5HT exerts an excitatory effect on the CRH secretion, with a resulting increase in ACTH and cortisol circulating levels (7). The activation of both 5HT2c (8) and $5HT_{1A}$/$5HT_{2A}$ receptors seems to mediate these neuroendocrine effects of 5HT (9-11).

In humans, serotonergic agonists have been shown to increase PRL, ACTH, and cortisol levels after acute administration (12-14) while the role of 5HT on GH secretion in physiological conditions is less clear (12, 13).

Based on this evidence, neuroendocrine challenge tests with serotonergic agonists have been often used to investigate the activity of the serotonergic system in both physiological and pathological conditions. The latter include psychiatric disorders, such as major depression and eating disorders, in which an impairment of serotonergic system as well as a central HPA hyperactivity have been demonstrated by most of the Authors (12, 13).

Besides psychiatric disorders, another condition characterized by serotonergic impairment and HPA alterations is aging, in which a decrease in 5HT concentrations has been demonstrated (15, 16). Many studies have also emphasized the existence of receptor loss in this period of life, as pointed out by both *post mortem* and *in vivo* analyses (17, 18) by using 5HT ligands and neuroimaging (19-21). The extent of 5HT receptor loss is reported to be 10-17% "per decade" starting from the levels at 20 yr of age (20-22). The most involved receptor subtypes are $5HT_{1A}$ and $5HT_{2A}$, while no clear reduced affinity of the remaining receptors has been described (20-23). Indeed, Sheline and co-workers (21) have shown that the age-related serotonergic receptor loss (especially for $5HT_{2A}$) is greatest in middle age, then levelling off after the 5th decade, in widely scattered brain regions, including the hippocampus. This suggests that middle age is a crucial period of life for the change in the neuroendocrine control of 5HT. A decline in central 5HT activity, expressed as a reduced PRL response to both 5HT releasing agents and receptor agonists, has also been shown in elderly subjects (24-26). Moreover, a recent work indicated a positive correlation between allelic variants of the 5HT transporter gene, morning cortisol concentrations, and cognitive impairment in a population of elderly subjects (27), thus emphasizing the link between serotonergic activity, HPA axis, and brain function in aging.

Since the serotonergic probes used so far have been criticized with respect to their limited specificity for sero-

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tonergic system (28, 29), or raise safety concerns, as in the case of fenfluramine (30, 31), some authors have suggested citalopram (CT), a specific 5HT reuptake inhibitor (SSRI), as a suitable neuroendocrine probe to investigate the serotonergic function (14, 28-34).
In order to clarify the neuroendocrine effects of 5HT across lifespan, in the present study we assessed the responses of ACTH, cortisol, DHEA, PRL, and GH to iv CT administration in a group of healthy young, middle aged and elderly volunteers. In fact, while middle age is probably a crucial period of life for the changes in the serotonergic activity, the majority of previous studies evaluated the age-related neurohornomal response to 5HT selectively comparing young and elderly people only.

SUBJECTS AND METHODS

Subjects

Twelve male young adults (YA) [age 29.2±1.7 yr mean±SEM, body mass index (BMI) 22.3 kg/m^2], 12 male middle aged (MA) (54.3±0.9 yr, BMI 23.7 kg/m^2) and 12 male elderly (ES) (69.3±0.9 yr, BMI 24.2 kg/m^2) subjects were studied. All the subjects were screened to exclude acute physical illness or any acute or prior psychiatric disorder by physical examination, laboratory testing, and structured interview. None of the subjects had history of alcohol, substance dependence or recent stress events. They had been free of any drug known to influence HPA axis and serotonergic system, especially antidepressants or neuroleptics, for at least 3 months before the study. The study protocol had been approved by an independent, local Ethics Committee and written, informed consent was obtained from all subjects.

Study design

All the subjects were randomized to receive placebo (saline iv over 120 min) or CT (20 mg iv over 120 min) with a 1-week washout between treatments. CT infusion was slower that in previous studies, in order to avoid side effects (like nausea, sickness, dizziness, distress, and restlessness) experienced with faster infusions (10 or 20 mg over 15-30 min) (28, 30, 35, 36).
After an overnight fasting, the tests began in the morning at 08:30-09:00 h, 30 min after an indwelling catheter had been placed into an antecubital vein of the forearm, that was maintained patent until the end of the study by slow infusion of isotonic saline.
Blood samples were taken every 15 min from 0 (starting of placebo or CT infusion) to +240 min for all the subjects. ACTH, cortisol, DHEA, PRL, and GH levels were analyzed at each time point.

Hormone measurements

Plasma ACTH levels (pg/ml) were measured in duplicate by a immunoradiometric assay (IRMA CTK, DiaSorin, Vercelli, Italy). The sensitivity of the assay was 1.2 pg/ml. The range of inter- and intra-assay coefficients of variations were 4.4-16.2% and 1.3-7.9%, respectively.
Serum cortisol levels (µg/l) were measured in duplicate by a radioimmunometric assay (RIA, Immunotech, France). The sensitivity of the assay was 3.62 µg/l. The range of inter- and intra-assay coefficients of variations were 5.3-9.2% and 2.8-5.8%, respectively.
Serum DHEA levels (µg/l) were measured in duplicate by a radioimmunometric assay (RIA, Chematil, Webster, Texas, USA). The sensitivity of the assay was 0.09 µg/l. The range of inter- and intra-assay coefficients of variations were 10.68-13.72% and 5.2-6.4%, respectively.
Serum GH levels (µg/l) were measured in duplicate by a immunoradiometric assay (IRMA CT, Radim, Pomezia, Italy). The sensitivity of the assay was 0.04 µg/l. The range of inter- and intra-assay coefficients of variations were 4.6% and 3.7%, respectively.
Serum PRL levels (µg/l) were measured in duplicate by a immunoradiometric assay (IRMA, Immunotech, France). The sensitivity of the assay was 0.5 µg/l. The range of inter- and intra-assay coefficients of variations were 6.2-8.0% and 1.6-2.8%, respectively.

Statistical analysis

Hormonal responses are expressed as mean, SEM, and relative 95% confidence interval (95% CI) of either absolute values or area under curves (AUC) calculated by trapezoidal integration. For each subject the differences between placebo and CT were computed at each time point and analysis of variance for repeated measures model (Greenhouse-Geisser estimation) was used to analyse the variation of the differences among YA, MA, and ES subjects in the 4 h of hormonal evaluation. Variations between placebo and CT effects at each time point and differences between YA, MA, and ES subjects (separately for placebo and CT) were compared by means of non-parametric Wilcoxon and Mann-Whitney test, respectively. Differences with a *p*-value <0.05 were considered statistically significant. SPSS (Statistical Package for the Social Science), version 15.0 was used for the analysis.

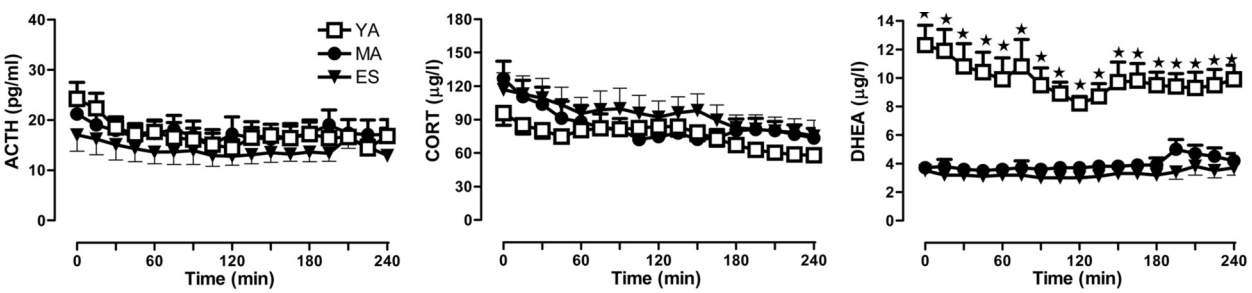

Fig. 1 - *ACTH, cortisol, and DHEA levels (mean±SEM) during placebo in young adults (YA), middle aged (MA), and elderly (ES) subjects.*

Table 1 - *GH, PRL, and DHEA area under curves (AUC_{0-240}±SEM during placebo or citalopram infusion in young adults (YA), middle aged (MA) and elderly (ES) subjects.*

AUC_{0-240}±SEM	YA	MA	ES
Placebo			
GH µg/l/h	183.8±111.8	172.6±115.4	142±14.9
PRL µg/l/h	1251.3±195.3	1140.5±88.1	1082.8±8.1
DHEA µg/l/h	2358.2±191.3	838.3±94.4	704.5±62.5
Citalopram			
GH µg/l/h	209.1±60.7	194.3±132.3	169.9±17.3
PRL µg/l/h	1299.9±333.5	1184.5±101.2	1123.4±94.4
DHEA µg/l/h	2416.4±158.4	865.8±211.4	749.8±109.3

RESULTS

During placebo session, a trend toward a decrease in the ACTH and cortisol levels were observed in all groups, without any significant difference recorded between each group (Fig. 1). On the contrary, DHEA levels were significantly higher ($p<0.001$) in YA compared to MA and ES at each time point; the two latter groups showed similar hormonal levels (Fig. 1). There were no statistically significant differences among the groups for GH and PRL levels (Table 1).

Looking at the CT effect, in YA ACTH concentrations were significantly increased by CT starting from time point 60 min up to 120 min ($p<0.05$) compared to the same time points during placebo session; cortisol secretion reached a significant increase ($p<0.05$) at 30 min, 45, and 60 min (Fig. 2). In MA, CT significantly increased ACTH starting from 15 min up to 165 min ($p<0.01$) and cortisol from 30 min up to 195 min ($p<0.01$) compared to placebo session (Fig. 2). In ES, ACTH levels were also significantly higher during CT ($p<0.01$) than during placebo, starting from 45 min up to 135 min, while cortisol levels were increased from 45 min up to 75 min ($p<0.05$) (Fig. 2).

No significant differences in GH, PRL, and DHEA secretion were observed between CT and placebo session in any group, although DHEA levels showed a trend toward increase during CT, especially in MA group (Table 1).

For CT session, an interaction effect of group has been recorded. YA *vs* MA: ACTH levels were significantly higher in MA from 30 min up to 90 min ($p<0.05$), while cortisol showed an even higher significant increase in MA, starting from 15 min to 195 min ($p<0.01$) (Fig. 3). YA *vs* ES: no differences were observed for ACTH, while cortisol was significantly higher in ES from 15 min up to 75 min ($p<0.05$) (Fig. 3). MA *vs* ES: ACTH levels were higher in MA from 15 min to 90 min and at 225 min and 240 min ($p<0.01$), while cortisol showed a significant higher increase in MA from time 60 min to time 180 min ($p<0.05$) (Fig. 3).

The statistical difference recorded for DHEA levels, which was higher at every time point in YA with respect to MA and ES ($p<0.001$) simply reflected the higher levels in YA already observed during placebo, as no response to CT has been shown in any group (Table 1). There were no statistically significant differences among the groups for GH and PRL levels (Table 1).

Side effects

CT administration induced a transient local discomfort (burning sensation at the beginning of the infusion) in 1 YA and 2 ES.

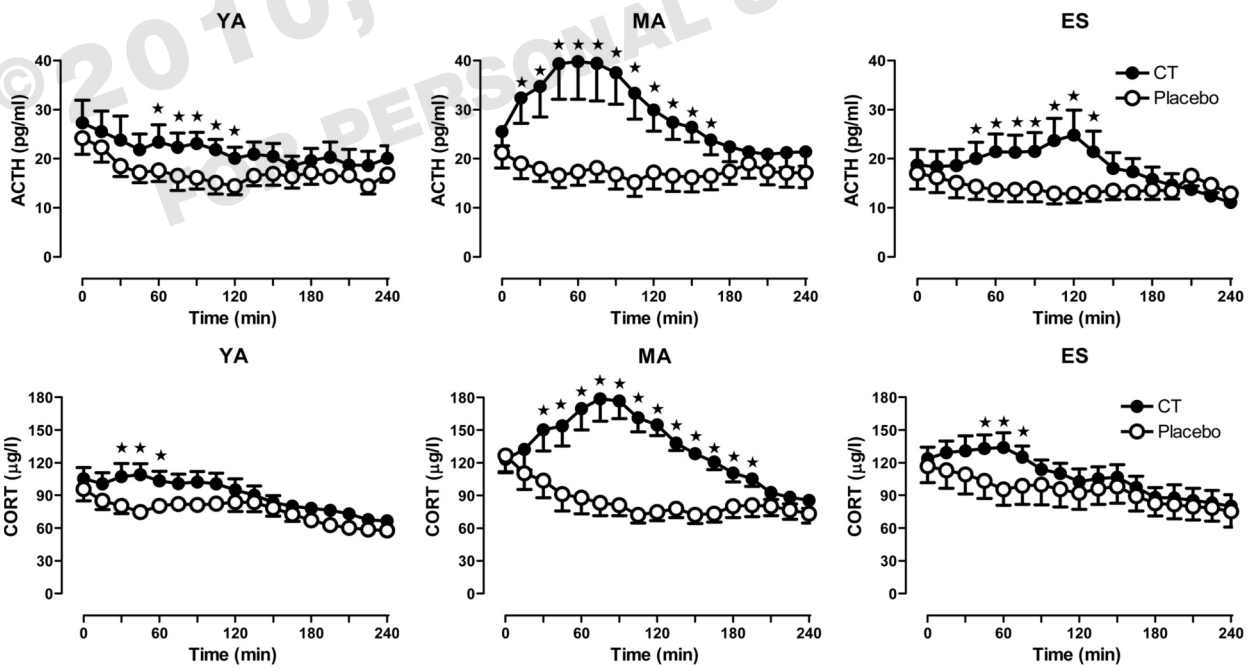

Fig. 2 - *ACTH and cortisol levels (mean±SEM) in young adults (YA), middle aged (MA), and elderly (ES) subjects during placebo and citalopram (CT) infusion.*

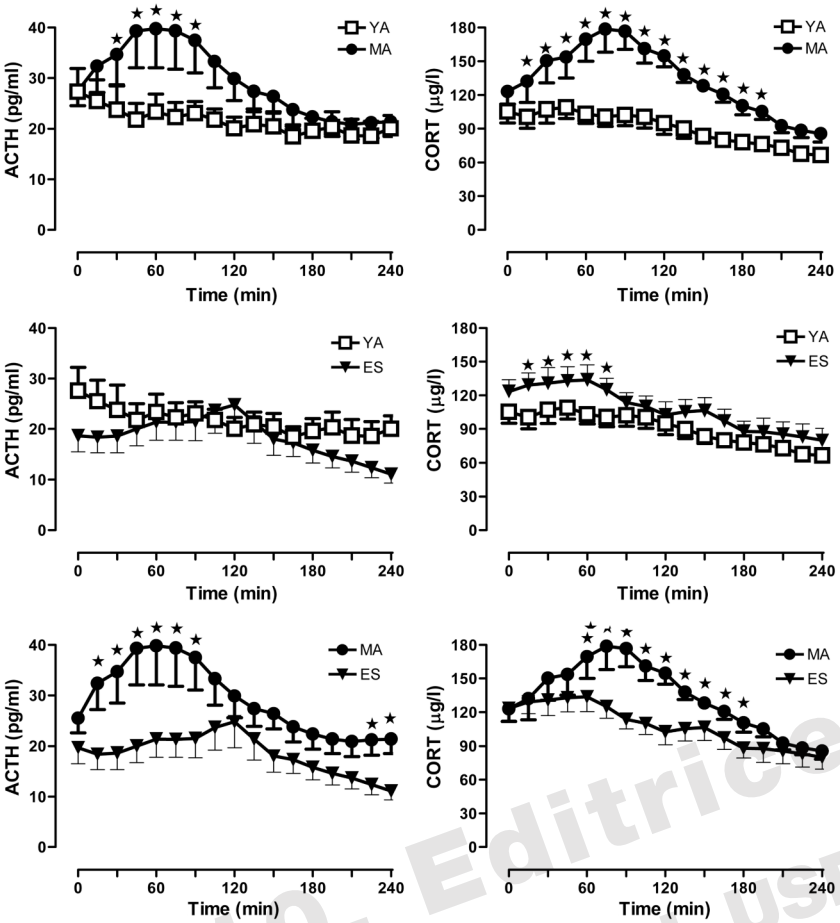

Fig. 3 - *ACTH and cortisol levels (mean±SEM) during citalopram (CT) infusion in young adults (YA), middle aged (MA), and elderly (ES) subjects.*

DISCUSSION

The results of our study demonstrate an age-dependent stimulatory effect of CT on corticotrope secretion in normal men. In fact, both ACTH and cortisol levels were significantly increased by acute CT infusion in YA, MA, and ES subjects, but a transient HPA hyper-responsiveness to CT has been recorded in MA, with hormonal levels clearly higher than in YA and ES subjects. Our findings also showed that DHEA secretion is clearly reduced starting from middle age, with no response to SSRI administration. Conversely, basal lactotrope and somatotrope activities were similar in all groups and no response to CT was observed in any period of adult life.

An age-related hyperactivation of HPA axis has been shown in both animals and humans, as demonstrated by the evidence of an increase in both basal and stimulated ACTH and cortisol concentrations in aging (37-40). However, some studies failed to observe any significant effect of age on either ACTH or cortisol levels (41-44) or even showed a decreased basal cortisol secretion with advancing age (45, 46). In agreement with these studies, we did not observe any significant age-related difference in term of morning basal ACTH and cortisol levels. This is not surprising, considering that the hyperactivation of HPA axis in the elderly is mostly occurring not at the peak level but rather during the nadir of the circadian rhythm, likely reflecting the age-related reduction in the negative feedback action of circulating glucocorticoids (37-39).

In humans, a stimulatory effect on both ACTH and cortisol secretion has been demonstrated after acute administration of several serotonergic agonists (12-14, 32). CT has been shown as a selective SSRI, with no known intrinsic activity at 5HT receptors or other receptor families (28, 30, 32) and it has been suggested as a suitable neuroendocrine probe to evaluate the central serotonergic activity (14, 28-34). The SSRI-induced inhibition of 5HT reuptake increases 5HT levels in the synaptic cleft, thereby prolonging the activation of post-synaptic 5HT receptors. We have previously demonstrated that acute serotonergic stimulation by citalopram increases ACTH and PRL levels in normal young subjects while some alterations in the neuroendocrine response to this compound was present in anorexic patients (47).

While a reduction in 5HT function as well as a derangement in the neuroendocrine response to 5HT has been demonstrated in aging, little information is available about the period of life in which serotonergic neuroendocrine activity starts to change.

Our findings showed that the corticotrope response to SSRI clearly changes across lifespan in normal men, starting

from middle age. The ACTH and cortisol responses to CT were, in fact, clearly amplified in MA subjects, whereas only cortisol response was significantly increased in aged subjects, in comparison with YA. These results seem, apparently, in contrast with the progressive reduction of 5HT function observed with advancing age and, especially, with the evidence of a marked 5HT receptors loss in middle age (20-22). Nevertheless, it may be hypothesized that, during this period of life, the 5HT receptor loss in the synaptic cleft leads to an up-regulation of the remaining receptors, with a resulting temporary hypersensitivity to serotonergic challenges. On the other hand, the progressive reduction in the HPA response to CT from middle to advanced age agrees with the hypothesis that the up-regulation mechanism is turned-off with advancing age, probably reflecting an age-related sensitivity loss of the remaining receptors. Moreover, a reduction of 5HT concentrations and/or a decrease in 5HT transporter concentrations, demonstrated in aged brain (15, 16), could also explain the progressive reduction in the HPA response to CT from middle to advanced age observed in our study.

Taking into account the evidence of the age-related decline in the brain 5HT activity, the basically similar HPA response to CT, in our YA and ES subjects was quite unexpected and not easy to explain. At a first glance, this finding could allow to state that advanced age may have no major impact on SSRI-induced HPA stimulation. However, the lack of remarkable difference in the hormonal response between YA and ES, observed in our study, may be consistent with the reduced responsiveness of the HPA axis to the negative feedback of the ES, leading to a relative HPA hyperactivity, which may mask the age-related decline in the 5HT function.

Moreover, in both YA and ES subjects, but not in MA, the adrenal response to CT was slightly anticipated or concomitant with the corticotrope response to the drug; this hormonal pattern is not usual for central stimulations which normally release ACTH before cortisol (48). Although SSRI receptors have been identified in both normal and hyperplastic adrenal gland, data in humans showed a direct stimulatory effect of SSRI in bilateral ACTH-independent bilateral macronodular adrenal hyperplasia only, possibly reflecting the increased *zona fasciculata* expression or abnormal function of "eutopic" 5-HT_4 receptor (48). However, a possible age-related sensitivity of normal adrenal gland to direct SSRI stimulation cannot be ruled out, although our present data could simply reflect the small number of subjects enrolled in our study.

Interestingly, we also found a precocious decline in DHEA secretion across lifespan, starting from middle age, where the hormonal levels were similar to those in aging. This indicates that the reduction in DHEA synthesis and secretion, which has been hypothesized to reflect a selective age-related atrophy of the reticularis zone (46), starts before aging. DHEA secretion is usually very sensitive to the increase in ACTH concentrations, either after administration of exogenous ACTH or in response to endogenous ACTH release (49-51). In our study, in spite of a significant ACTH response to CT in all groups, no DHEA response was recorded, although a trend toward increase was observed in middle age, where ACTH reached the highest levels. This is likely to reflect the small number of subjects studied, although a direct action of serotonergic compounds on adrenal gland cannot be ruled out. Finally, our findings did not show a significant effect of CT infusion on either PRL or GH secretion across lifespan, in agreement with controversial data previously reported (12, 13). Concerning PRL secretion, a possible sex-related influence of SSRI on lactotrope function can be hypothesised. In fact, most previous studies, which demonstrated a significant PRL response to different 5HT-agonists, referred to females only, whereas no significant PRL response to D-fenfluramine was reported in males by some authors (52, 53). Moreover, two other possible explanations can be taken into account: first, we performed the test in the morning, while previous studies performed the test in the afternoon, to avoid the morning decline in plasma PRL and cortisol levels (28, 30, 35); second, the rate of CT infusion was smaller in our than in previous studies, which used faster infusion rates, up to 20 mg in 15 min (36).

In conclusion, our study demonstrated that corticotrope response to CT is age-dependent in normal men, being clearly amplified in middle age with a progressive decline with advancing age. This suggests precocious changes in the serotonergic neuroendocrine control during human lifespan, possibly reflecting age-related changes in 5HT receptor expression and/or sensitivity. These data also indicate that CT is a useful tool to evaluate the age-dependent serotonergic function in humans.

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Disclosure statement

Nothing to declare.

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