

EXPLORATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN THE AGED

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SUMMARY

In order to investigate the adrenocortical axis in aged people, we have evaluated adrenal function through different dynamic parameters. Seven healthy elderly patients, 4 women and 3 men, whose ages ranged from 70 to 91 years were studied; cortisol concentration in serum was evaluated at 8 a.m. and 4 p.m. (circadian rhythm) as well as the responses to inhibition (Nugent) and stimulation tests (synthetic ACTH and Calcium test). The cortisol levels at 8 a.m. and 4 p.m. were $15 \pm 3.5 \mu\text{g}/100 \text{ ml}$ and $7.5 \pm 1.92 \mu\text{g}/100 \text{ ml}$ respectively. The Nugent test showed a significant inhibition of cortisol ($p < 0.025$); the stimulation tests either with ACTH or Calcium caused a significant increase in circulating cortisol ($p < 0.005$).

The results obtained demonstrate both the normality of the basal concentration of cortisol and of the circadian rhythm and the response to the inhibition and stimulation tests. We can draw the conclusion that the aged person has an adequate reserve in the hypothalamic-pituitary-adrenal axis.

Several papers concerning the hypothalamic hypophyseal axis in old age have been published. Regulatory mechanisms, especially of the gonadotropin area, have been established; it has been investigated whether other hypophyseal hormones varied (in parallel to) the production of peripheral hormones. A vital gland, the adrenal gland, remains in apparent normality in the healthy aged. We attempted to investigate whether this axis remains normal under dynamic circumstances. Therefore, we put emphasis on the endovenous injection of calcium as a stimulus, in view of the importance that this ion possesses in hormonal secretion.

MATERIAL AND METHODS

A research-work on 7 healthy ambulatory elderly people (4 women and 3 men) whose ages ranged from 70 to 91 years, was carried out without medication. All of them were on the same diet and were hospitalized in a geriatric institution. The blood samples were taken by venopuncture at 8 a.m. in a fasting state. In each subject, both the plasma cortisol level at 8 a.m. and 4 p.m. (circadian rhythm) and the responses to the dexamethasone inhibition and to the ACTH and Calcium® (Sandoz) stimulation were evaluated. The Nugent test was carried out determining the morning cortisolemia with prior ingestion of 1 mg of dexamethasone at 11 p.m. the night before. Injections of 0.25 mg of synthetic ACTH and 20 ml of Calcium gluconate 10% (180 mg of ion Ca^{++}) for the stimulation tests were given by endovenous route. In both tests the plasma cortisol levels were determined before and 30 and 60 minutes after the injection. The determination of plasma cortisol was made by the Murphy method (protein competition) using 1-2 tritiated cortisol. (New England Nuclear Net 185). Normal values at 8 a.m. were 5-25 $\mu\text{g}\%$.¹ The statistical analysis was performed according to Student's test.

RESULTS

The basal cortisolemias (8 a.m.) were normal in 6 out of 7 patients studied; in one case (Table 1) the values were high. However, this patient showed good evidence of circadian rhythm variation and a satisfactory response to the inhibition with dexamethasone; in this patient another basal cortisolemia was within normal range. The mean \pm SE of the basal plasma cortisol was of 15 ± 3.5 , and at 4 p.m. it fell down to $7.5 \pm 1.92 \mu\text{g}/100 \text{ ml}$ ($p < 0.001$) (Fig. 1) which connotes a good function of the adrenal axis in the aged. The Nugent test shows a lowering of the cortisol level to values lower than $5 \mu\text{g}/100 \text{ ml}$ in 6 out of 7 patients studied; in one of them, the inhibition was insufficient. Analysis shows that the response was statistically significant ($p < 0.025$). With the synthetic ACTH stimulus, the response observed was greater at 30 min. In 5 out of 7 patients analyzed, and in the other two cases which had a greater elevation of the cortisolemia after 60 minutes, the basal values were doubled in both groups. In two cases the rise obtained was higher than $40 \mu\text{g}/100 \text{ ml}$. The stimulation was significant ($p < 0.0025$). In the Calcium test a good response was observed in 6 out of 7 cases studied. The other one (Table, case 1) showed an increase of only 40% in the serum cortisol in relation to the basal value, while the normal pattern accepted for the adult under 60, ranges between 48 and 135%. It is found through statistical analysis that the response is highly significant ($p < 0.005$).

The highest levels of cortisol under Calcium stimulus were observed after 60 minutes in 4 out of 7 patients, while in the other 3 cases it was found that the maximum response appeared 30 minutes after the administration of the drug, as it is usual in the adult under 60 years of age (Fig. 2).

Side effects were not observed during the test.

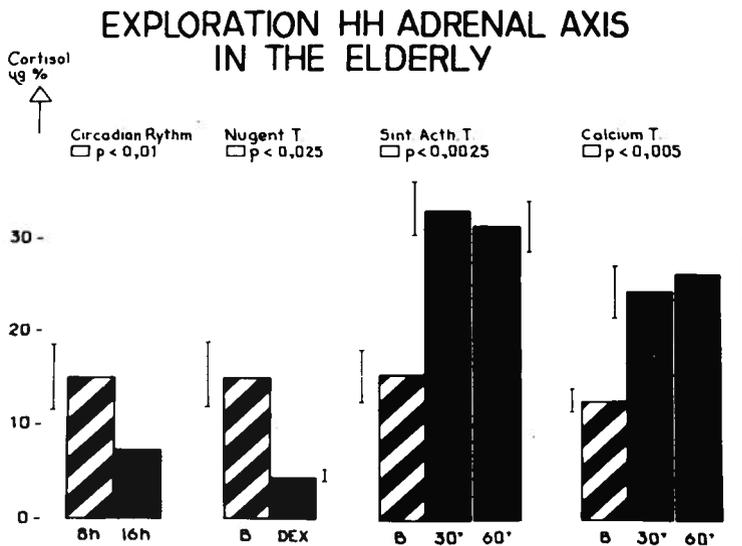


Fig. 1 — Results of the dynamic exploration of the hypothalamic-pituitary-adrenal axis of geriatric patients. The cortisol serum levels are shown as group means ($\mu\text{g}/100 \text{ ml}$) with the standard error indicated in the margin. The significance test is shown in the upper part of the graph.

Table 1
Individual variations of the serum cortisol ($\mu\text{g}/100\text{ml}$) obtained during different dynamic exploration tests

Case	Sex	Age	CORTISOL $\mu\text{g}/100\text{ml}$								
			Circadian rhythm		Nugent Test	ACTH Test			Calcium Test		
			8h	16h	8h	0min.	30min	60min.	0min.	30min	60min.
1	F	87	10.5	2.5	3.0	12.0	38.0	30.0	10.0	14.0	12.0
2	F	79	6.0	7.0	4.0	6.5	24.0	22.0	9.0	25.0	21.0
3	F	80	7.0	3.0	3.0	15.0	39.0	40	9.0	19.0	40.0
4	F	91	22.0	11.0	5.0	24.0	>40.0	40	18.0	30.0	40.0
5	M	70	7.5	3.0	3.0	8.0	26.0	35.0	14.0	38.0	24.0
6	M	72	30.0	18.0	4.0	29.0	>40.0	40.0	15.0	21.0	25.0
7	M	67	11.0	8.0	8.0	13.0	24.0	15.0	15.0	23.0	24.0
Mean \pm SE		78	15.0 \pm 3.5	7.5 \pm 1.92	4.29 \pm 0.63	15.36 \pm 2.86	33.0 \pm 2.71	31.71 \pm 2.64	12.7 \pm 1.20	24.3 \pm 2.73	26.6 \pm 3.54

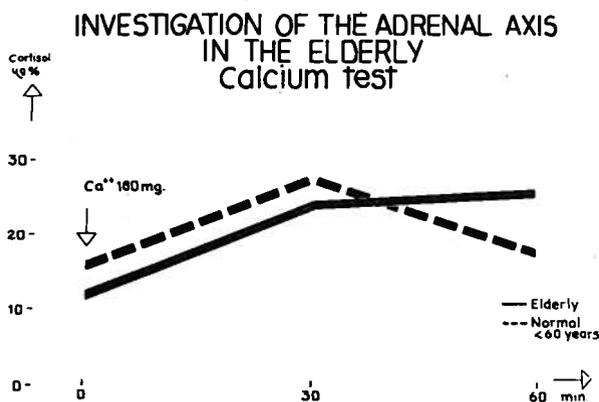


Fig. 2.— Comparison between the results obtained from the calcium test on geriatric patients and normal adults. The serum cortisol levels are shown in µg/100ml.

DISCUSSION

The circadian rhythm variations of cortisol, as well as the adrenal response to ACTH and the hypophyseal sensitivity to the inhibitory effect of dexamethasone in elderly people, do not differ from the results obtained in the normal adult,² as also stated by other workers.³⁻⁷ The contraindications of the use of lysine-vasopressine in the aged due to its cardiovascular effects is absolute. Neither the insulinic hypoglycemia nor the administration of pyrogens is advisable. These antecedents and the results obtained with the i.v. administration of Calcium gluconate in the adult led us to use this substance as an exploratory medium.

Among the 7 aged patients investigated with Calcium injection, 6 showed a satisfactory response similar to the normal adult, i.e. a significant rise in the cortisol level. Besides, 4 out of 6 showed persistence of elevated cortisol even after 60 minutes. This behaviour differs from that of the normal grown up, who reaches a maximum peak of cortisol after 30 minutes, with return to the basal value after 60 minutes (Fig. 2). We observe a similar pattern of response in the exploration of the senile thyrotropic,⁸ and somatotropic axis,⁹ without finding a clear explanation to this phenomenon.

The mechanism of action of the Calcium ion has not been fully elucidated. Previous papers,¹⁰⁻¹² show that with the administration of dexamethasone there is no increase in plasma cortisol with the Calcium stimulus. This seems to indicate an effect of this ion at the hypothalamic level. Besides, the abnormal responses observed in patients with extrasellar pathology lends support to the view that the preservation of certain hypothalamic areas and their perfect communication with the hypophysis are required to produce the Calcium stimulus. Hall,¹³ has pointed out a reduction in weight and adeno-hypophyseal histological variation in the aged but, others¹⁴ have not found any modifications in the hypophyseal content of ACTH, HGH and TSH.

The intraglandular increase in gonadotropins in women at the menopause is a well known fact. These results agree with the findings of our group which show an elevated hypophyseal reserve of gonadotropins¹⁵ and thyrotropin⁸ in both sexes. The prolactin axis, however, shows a capacity of response to the stimulation tests that is lower, though all the same significant, than that of the adult.¹⁶ In the adrenal glands of

the aged, microscopic alterations have been described, such as pigment accumulation, connective tissue proliferation and, in senile animals there are fragmentations and other alterations of the mitochondria.¹³ However, it is evident that the response capacity of the adrenal gland to the ACTH stimulus leads to a significant increase in cortisol similar to that of young adults indicating a good preservation of adrenal reserve.

CONCLUSIONS

The conservation of the aged hypophyseal functional reserve for the gonadotropic, prolactinic, somatotropic and thyrotropic axis has been sufficiently proved, in spite of some anatomical and histological alterations described.

In order to investigate the adrenocortical axis in aged people we have evaluated adrenal function through different dynamic parameters. Seven healthy, elderly patients — 4 women and 3 men — whose ages ranged from 70 to 91 years, were studied. Serum cortisol concentration was evaluated at 8 a.m. and 4 p.m. (circadian rhythm) as well as the response to inhibition with 1 mg of dexamethasone (T. Nugent). Cortisol levels at 8 a.m. and 4 p.m. were $15 \pm 3.5 \mu\text{g}/100 \text{ ml}$, and $7.5 \pm 1.92 \mu\text{g}/100 \text{ ml}$ respectively.

The Nugent test showed a significant inhibition of cortisol ($p < 0.025$). These results do not differ from those observed in the normal adults. As regards the stimulation tests, the use of 0.25 mg of synthetic ACTH in the adrenal pole caused a significant increase in serum cortisol as compared to the basal value ($p < 0.005$) which is similar to that observed in the adults.

In order to explore the hypophyseal-hypothalamic pole we have chosen the i.v. Calcium test due to its harmlessness, since other stimuli (insulinic hypoglycemia, lysine-vasopressin and pyrogens) are potentially risky in the aged, specially if they have cardiovascular or cerebrovascular antecedents.

The administration of 20 ml of Calcium gluconate 10% produced a significant increase in cortisol values ($p < 0.005$), in 6 out of 7 aged patients who were observed, with the special characteristic that the average values kept high after 60 minutes, in contrast to the normal adults who respond with a maximum peak after 30 minutes returning to the basal value after 60 minutes.

The sufficient response of plasmatic cortisol before the injection of Calcium ion together with the lack of secondary effects in all the studied patients, led us to suggest the incorporation of this test as a useful resort in the evaluation of the hypothalamic-pituitary adrenal axis in the aged.

RESUMO

A fim de estudar a função do eixo corticosuprarenal nos indivíduos idosos avaliou-se, por intermédio de determinados parâmetros dinâmicos, a função suprarenal. Sete indivíduos saudáveis e idosos, 4 mulheres e 3 homens de idades compreendidas entre os 70 e os 91 anos, tomaram parte no estudo; foi determinada a concentração de cortisol plasmático às 8 e às 16h (ritmo circadiano) e investigou-se a resposta aos testes de inibição (Nugent) e estimulação (ACTH sintético e Cálcio). Os níveis de cortisol às 8 e às 16h eram de $15 \pm 3,5 \mu\text{g}/100 \text{ ml}$ e $7,5 \pm 1,92 \mu\text{g}/100 \text{ ml}$ respectivamente. O teste de Nugent inibiu significativamente o cortisol ($p < 0,025$) enquanto que os testes de estimulação quer com ACTH quer com Cálcio aumentaram substancialmente os níveis circulantes desta hormona ($p < 0,005$).

Os resultados obtidos atestam a normalidade das concentrações basais de cortisol e do ritmo circadiano bem como da resposta aos testes de inibição e estimulação. De tudo isto pode concluir-se que os indivíduos idosos possuem uma reserva funcional adequada do eixo hipotálamo-hipófise-suprarenal.

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