Enhancement of gonadotrophin induced 17,20-lyase suppression one week after human chorionic gonadotrophin priming


Department of Medicine, Division of Endocrinology, University of Nijmegen, The Netherlands

Abstract. A single injection of 1500 IU of human chorionic gonadotrophin (hCG) in normal men, induced a block in the conversion of 17-hydroxypregosterone (17-OHP) to testosterone (T) which reached its maximum 24 h after hCG loading. One week after hCG administration both basal 17-OHP (3.8 ± 0.6 vs 5.1 ± 0.5 nmol/l; P < 0.02) and T levels (15.1 ± 1.7 vs 18.5 ± 2.3 nmol/l; P < 0.05) were about 20% lower than before hCG exposure. The ratio 17-OHP to T (0.29 ± 0.04 vs 0.31 ± 0.04, P > 0.10) was however similar, suggesting recovery from the prior 17,20-lyase suppression at a lower overall capacity of T synthesis. hCG administration one week after the priming dose elicited an increase in the ratio 17-OHP to T, which was about twice as high as after the first hCG injection. Together the data suggest: 1) suppression of testicular steroidogenesis proximal to 17-OHP one week after hCG priming, 2) enhanced hCG induced 17,20-lyase suppression one week after hCG exposure.

Administration of a single dose of human chorionic gonadotrophin (hCG) induces a transient accumulation of 17-hydroxypregosterone (17-OHP) relative to testosterone (T) starting 4 h after the injection and reaching its maximum after 14 h (Saez & Forest 1979; Forest et al. 1979; Smals et al. 1980a,b,c; Wang et al. 1980). This inappropriate rise of 17-OHP has been attributed to oestrogen (?) mediated suppression of 17,20-lyase enzymatic activity (Smals et al. 1980c,d; Cigorraga et al. 1980). Return of the 17-OHP/T ratio to pre-treatment levels or even lower (Smals et al. 1980a,b) at 72 h, suggests a recovery of the 17,20-lyase enzymatic activity. Indeed Chasalow et al. (1979) in an in vitro experiment in rats demonstrated recovery of both 17,20-lyase and also 17-hydroxylase activity to start 48 h after the hCG injection and to be almost complete at 96 h.

The observation of subnormal basal 17-OHP and T levels one week after a single hCG injection prompted us to study the delayed (24, 48, 72 h) response of both steroids to renewed hCG administration one week later, and we found enhanced suppression of 17,20-lyase activity which was maximal after 24 h. During the preparation of this manuscript Glass & Vigersky (1980) also reported significant suppression of basal plasma T and an enhanced acute (4 h) response of 17-OHP to hCG 10 days after gonadotrophin priming. These investigators however, did not find depressed 17-OHP levels and from their data they suggested persistence of the 17,20-lyase block. Our data do not favour persistence of 17,20-lyase suppression but rather enhancement of 17,20-lyase block by renewed hCG administration one week after hCG priming.

Materials and Methods

Ten normal laboratory personnel, who had all fathered children, age 33 ± 4 years (range 20–56 years) volunteered in this study after prior informed consent. At 9 a.m. on day 1 and 8 all subjects were given 1500 IU of hCG (Pregnyl®, Organon) im and on both occasions blood for 17-OHP and T assay was sampled immediately before

Requests for reprints:
A. G. H. Smals, Department of Medicine, Division of Endocrinology, University of Nijmegen, Geert Grooteplein 16, Nijmegen, the Netherlands.
and exactly at 24, 48 and 72 h after the single injection. Plasma 17-OHP and T levels were measured by RIA after a paper chromatographic purification step using antisera raised in sheep against 11-deoxycortisol-21-hemisuccinate and in rabbits against 11-deoxycortisol-11-hemisuccinate conjugated to albumin (Smals et al. 1976, 1978). The intra-assay coefficients of variation were 4 and 6.1%, respectively. To avoid inter-assay variation all samples from one subject were measured in the same assay.

Statistical analysis was performed using Student’s paired t-test. The mean values ± 1 SEM are given.

Results

Basal 17-OHP and T levels and the ratio 17-OHP to T before the first and second hCG injection (Fig. 1)

The mean basal 17-OHP and T levels immediately before the second injection of hCG were significantly lower than before the priming dose (3.8 ± 0.6 vs 5.1 ± 0.5 nmol/l, P < 0.02 and 15.1 ± 1.7 vs 18.5 ± 2.3 nmol/l, P < 0.05), but the mean ratio of 17-OHP to T was similar (0.29 ± 0.04 vs 0.31 ± 0.04, P > 0.10).

Effect of two separate hCG injections on 17-OHP, T and the ratio of 17-OHP to T (Figs. 1 and 2)

Single hCG administration increased 17-OHP levels at 24, 48 and 72 h after the first injection to 2.1 ± 0.2 (P < 0.001), 1.9 ± 0.2 (P < 0.001) and 1.5 ± 0.2 (P < 0.001) times the baseline value, respectively, whereas T levels rose to 1.5 ± 0.1 (P < 0.001), 1.7 ± 0.1 (P < 0.001) and 1.8 ± 0.2 (P < 0.01) times the pre-treatment level. Thus between 24 and 72 h after hCG injection 17-OHP and T ran a dissociated course with T rising and 17-OHP falling. A transient accumulation of 17-OHP relative to T as reflected by an elevated 17-OHP/T ratio, 1.5 ± 0.1 times baseline (P < 0.001 vs t = 0) was noted at 24 h. Thereafter the ratio decreased to 1.1 ± 0.1 at 48 h (P > 0.10 vs t = 0) and 0.8 ± 0.1 at 72 h (P > 0.10 vs t = 0).

Before the second hCG injection the mean basal 17-OHP and T levels were significantly lower than before the priming dose. As in the first experiment maximum 17-OHP levels were achieved 24 h after the second injection of hCG (10.2 ± 0.9 ng/100 ml vs 10.0 ± 0.7 nmol/l). Although the absolute maximum increase of 17-OHP tended to be higher after the second injection (6.8 ± 0.9 vs 5.2 ± 0.7 nmol/l) the difference was not statistically significant (0.05 < P < 0.10). The mean relative increase of 17-OHP after the second hCG injection however was significantly higher than after the priming dose (3.4 ± 0.6 vs 2.1 ± 0.2 times baseline, P < 0.025).
The effect of human chorionic gonadotrophin administration (Pregnyl®, Organon, 1500 IU im) on the mean percentage 17-hydroxyprogesterone (17-OHP) and testosterone (T) levels ± 1 SEM and the ratio 17-OHP to T before (○---○) and one week after (●——●) hCG priming. The asterisks indicate statistically significant differences between the first and second hCG injection: *P < 0.10. **P < 0.02. ***P < 0.01.

As in the first experiment maximum plasma T levels were achieved 72 h after the second injection. Although the mean T levels achieved 24, 48 and 72 h after the second injection of hCG remained significantly lower than in the first experiment (20.6 ± 1.9 vs 26.2 ± 2.2 nmol/l at 24 h, P < 0.01, 26.0 ± 2.5 vs 31.7 ± 2.6 nmol/l at 48 h, P < 0.02 and 26.1 ± 2.6 vs 32.4 ± 2.7 nmol/l at 72 h, P < 0.01) the mean maximum absolute (12.2 ± 2.0 vs 15.0 ± 1.7 nmol/l) and relative 81.9 ± 0.1 vs 1.9 ± 0.2) increments were of the same order of magnitude (P > 0.10). Despite almost similar basal 17-OHP to T ratios before the first and second injection of hCG (0.31 ± 0.04 and 0.29 ± 0.04), the mean 17-OHP to T ratio 24 h after the second injection (0.60 ± 0.06, 2.3 ± 0.3 times baseline) was significantly higher (P < 0.02) than after the priming dose (0.46 ± 0.05, 1.5 ± 0.1 times baseline, P < 0.01). The mean increment in the 17-OHP to T ratio 24 h after the second injection (0.30 ± 0.04) was about twice as high as after the first injection (0.15 ± 0.03, P < 0.001). At 48 and 72 h no statistically significant differences in the 17-OHP to T ratios could be demonstrated (0.34 ± 0.04 vs 0.39 ± 0.05 and 0.26 ± 0.02 vs 0.28 ± 0.03, respectively, P > 0.10).

Discussion

Earlier we reported that after a single injection of hCG, plasma 17-OHP and T values run a dissociated course: a more pronounced rise of 17-OHP relative to T after 24 h followed by a further rise of T with falling 17-OHP levels (Smals et al. 1980a,b). This finding was interpreted to indicate a transient blockade in the Δ4 biosynthetic pathway at the 17,20-lyase.

In this study it was shown that a second injection of hCG 7 days after the first, disclosed patterns of plasma 17-OHP and T levels in two ways different from those after the priming dose: 1) the basal 17-OHP and T levels were significantly reduced by about 20% with an almost identical 17-OHP to T ratio, 2) a more pronounced increase of 17-OHP relative to T occurred 24 h after the second hCG injection than after the priming dose, the increase of the 17-OHP to T ratio at that moment being about twice the increase after the first injection of hCG.

Lowered plasma 17-OHP and T levels to equal proportions 7 days after hCG priming point to a long lasting effect of hCG early in the biosynthetic pathway prior to 17-OHP. Glass & Vigersky (1980) very recently reported a similar lowering of plasma T levels 10 days after a priming dose of hCG in normal men. These investigators however, did not find similarly decreased 17-OHP levels. They concluded therefore from their data that the block in the conversion of 17-OHP into T still persisted after 10 days. Scrutinizing the data of Glass & Vigersky (1980) we calculated from their figures of the mean 17-OHP and T levels a similarly un-
changed 17-OHP to T ratio (0.20 and 0.19, respectively) before the first and second hCG injection. Thus in contrast to their own interpretation the data do not favour persistence of the block in conversion of 17-OHP to T 10 days after hCG priming. Yet the possibility that a 17,20-lyase block may be present too modest to affect the 17-OHP/T ratio which only becomes fully apparent after hCG loading cannot be excluded. Nevertheless, our data are in accordance with in vitro findings of Chasalow et al. (1979) in rats demonstrating almost complete recovery of 17,20-lyase and also hydroxylase activities 96 h after hCG administration.

Although one can only speculate on the mechanism underlying the 17-OHP and T suppression 7 days after hCG priming the about equal suppression of both steroids suggests that the lesion must be localized at a locus proximal to 17-OHP and probably proximal to progesterone (Chasalow et al. 1979). Lack of receptor availability resulting in decreased pregnenolone formation (Cigorraga et al. 1978; Catt & Dufau 1978) cannot simply account for the reduction of basal 17-OHP and T levels, as in rats a return of the T response to gonadotrophin administration to normal has been demonstrated 5 days after hCG loading when only a few per cent of the LH receptors had just begun to return.

Despite indirect evidence of recovery of the 17,20-lyase enzymatic activity, repeated hCG administration 7 days after gonadotrophin priming — when hCG has reportedly virtually disappeared from the circulation (Saez & Forest 1979; Martikainen 1981) — induced a more pronounced increase of 17-OHP relative to T 24 h after the second hCG dose than after the first injection. As the absolute and relative T increments were similar in both experiments, the increase in the ratio of 17-OHP relative to T 24 h after the second injection was about twice the increase observed after the priming dose. Glass & Vigersky (1980) demonstrated that this difference in 17,20-lyase block between the first and second dose of hCG was already present as early as 4 h after the injection. The data presented in this study extend these observations. Maximum enhancement of the 17,20-lyase block was observed 24 h after the second injection of hCG, whereas at 48 and 72 h this transient enhancement was no longer discernible. Preliminary data from our laboratory in 6 normal men suggest that 14 days after hCG priming, basal and stimulated plasma 17-OHP and T levels do not longer differ from those obtained immediately before and after the first hCG injection.

In contrast with the presumptions of Glass & Vigersky (1980) who assumed persistence of the 17,20-lyase block for at least 10 days after hCG exposure, the present data suggest that renewed hCG administration 7 days after hCG priming enhances the 17,20-lyase block, despite apparent prior recovery of the enzymatic activity.

The mechanism operative in the enhancement of the hCG induced 17,20-lyase block 7 days after hCG exposure is not known. Very recently Chasalow & Marr (1980) reported the occurrence of an inhibiting protein in rats, suppressing 17,20-lyase activity, as early as 2 h and as long as 65 h after single hCG administration. One might speculate that hCG priming facilitates the formation of such an inhibitor in response to the second hCG injection. Augmentation of hCG induced oestrogen production after gonadotrophin priming either by increased induction of aromatase (Valladares & Payne 1979) or enhanced direct testicular secretion might also account for the more pronounced 17-OHP accumulation relative to T after renewed hCG administration. Preliminary data from our laboratory of almost similar circulating oestradiol levels both before and after the priming dose and the second injection of hCG however do not favour such a hypothesis.

References


Received on June 5th, 1981.