

## Supplementary Materials

**Table S1.** Summary of the investigations into the origin of 11OHA4.

| Tissue/specimen             | Administered                       | Steroid isolated                  | Hypotheses/Conclusions                                                                               | Reference |
|-----------------------------|------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------|-----------|
| Bovine adrenals (perfusion) | A4                                 | 11OHA4;<br>11OH-5 $\alpha$ -dione | • A4→11OHA4→11KA4                                                                                    | [2]       |
| Human urinary samples       | 11KA4 (C19)                        | 11OHA4:5 $\alpha$ > 5 $\beta$     | • C19 steroids→ primarily 5 $\alpha$ -stereoisomere of 11OHA4                                        | [3]       |
|                             | Cortisol (C21)                     | 11OHA4:5 $\alpha$ < 5 $\beta$     | • C21 steroids→ primarily 5 $\beta$ -stereoisomere of 11OHA4                                         |           |
|                             | Cortisone (C21)                    | 11OHA4:5 $\alpha$ < 5 $\beta$     |                                                                                                      |           |
|                             | 21-desoxycortisone (C21)           | 11OHA4:5 $\alpha$ < 5 $\beta$     |                                                                                                      |           |
| Human adrenals              | Corticotropin                      | 11OHA4                            | • 11OHA4 is produced in the human adrenal                                                            | [1]       |
| Human urinary samples       | A4 (C19)                           | AST:5 $\alpha$ = 5 $\beta$        | • C19 steroids (and not C21)→5 $\alpha$ -stereoisomere of AST                                        | [4]       |
|                             | T (C19)                            | AST:5 $\alpha$ = 5 $\beta$        | • 11KA4, 11OHA4→primarily 11OHA4                                                                     |           |
|                             | DHEA (C19)                         | AST:5 $\alpha$ = 5 $\beta$        |                                                                                                      |           |
|                             | 17OH-PROG (C21)                    | AST:5 $\alpha$ < 5 $\beta$        |                                                                                                      |           |
| Human adrenals              | PREG                               | 11OHA4 (no A4 or DHEA)            | • Cortisol→11OHA4<br>• 17OH-PROG→ A4→11OHA4                                                          | [13]      |
| Human adrenals              | Radiolabeled PROG, DHEA, 17OH-PREG | A4; 11OHA4, DHEA                  | • PREG→ 17OH-PREG→DHEA→A4 ( $\Delta^5$ -pathway)<br>• A4→11OHA4<br>• Deoxycortisol, cortisol→ 11OHA4 | [5]       |
| Human adrenals              | Radiolabeled T                     | A4; 11KA4; 11OHA4; 11OHT          | • A4→11OHA4<br>• 11OHT→11OHA4                                                                        | [16]      |
| Human adrenals              | Radiolabeled PROG                  | 11OHA4                            | • PROG→ negligible 11OHA4                                                                            | [6]       |

Table S1. Cont.

| Tissue/specimen                                        | Administered                                                       | Steroid isolated                            | Hypotheses/Conclusions                                                     | Reference                                                                                  |
|--------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Urinary samples                                        | Radiolabeled 11OHA4<br>Radiolabeled 11KA4<br>Radiolabeled cortisol | 11-oxy-17-ketosteroids                      | 5 $\alpha$ > 5 $\beta$<br>5 $\alpha$ > 5 $\beta$<br>5 $\alpha$ < 5 $\beta$ | • Primarily C19 steroids→5 $\alpha$ -stereoisomers of 11-oxygenated 17-ketosteroids<br>[8] |
| Urinary samples                                        | Radiolabeled ATHF (5 $\alpha$ -derivative of cortisol)             | 11OHA4; 11KA4                               | • ATHF→negligible 5 $\alpha$ -stereoisomers                                | [9]                                                                                        |
| Human adrenals                                         | Radiolabeled DHEA, PROG, cortisol (in combinations)                | 11OHA4                                      | • Primarily DHEA→11OHA4<br>• Cortisol→11OHA4                               | [14]                                                                                       |
| Baboon adrenals (perfusion); human and baboon adrenals | A4<br>Cortisol                                                     | 11OHA4<br>Low levels of 11OHA4              | • Primarily A4→11OHA4                                                      | [10]                                                                                       |
| Human adrenals: microsomal and mitochondrial fractions | Radiolabeled deoxycortisol<br>Radiolabeled DOC                     | Cortisol; A4; 11OHA4 (no cortisone)<br>CORT | • Cortisol cleavage in only the microsomal fraction                        | [15]                                                                                       |
| COS-1 cells (transfected with human CYP17A1)           | PROG<br>PREG                                                       | 17OH-PROG (no A4)<br>17OH-PREG; DHEA        | • PROG, 17OH-PROG→A4                                                       | [7]                                                                                        |

5 $\alpha$ -5 $\alpha$ , 5 $\beta$ -5 $\beta$ , A4-androstenedione, AST-androsterone, ATHF-11 $\alpha$ -tetrahydrocortisol, CORT-corticosterone, CYP17A1-cytochrome P450 17 $\alpha$ -hydroxylase/17-20 lyase, DHEA-dehydroepiandrosterone, DOC-deoxycorticosterone, PREG-pregnenolone, PROG-progesterone, 11KA4-11 $\beta$ -ketoandrosterone, 11OHA4-11 $\beta$ -hydroxyandrostenedione, 11OHA4-11 $\beta$ -hydroxyandrostenedione, 11OH-5 $\alpha$ -dione-11 $\beta$ -hydroxy-5 $\alpha$ -androstenedione, 11OHT-11 $\beta$ -hydroxytestosterone, 17OH-PREG-17 $\alpha$ -hydroxypregnenolone, 17OH-PROG-17 $\alpha$ -hydroxyprogesterone.