HPA axis modulation by a potent inhibitor indicates 11β-hydroxysteroid dehydrogenase type 1 (HSD-1) is a significant contributor to cortisol levels

RF21 | PSAT100

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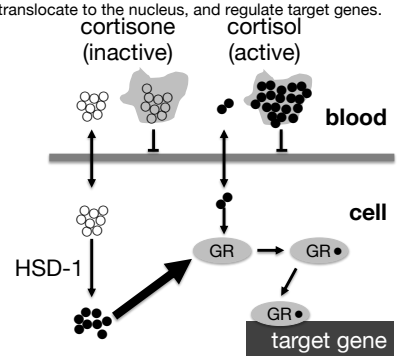
11β-HYDROXYSTEROID DEHYDROGENASE (HSD) ENZYMES AND CLINICAL ASSAYS FOR THEIR ACTIVITY

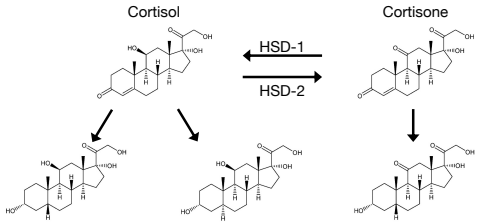
The HSD enzymes control intracellular levels of cortisone & cortisol.

- HSD-1 converts inactive cortisone to active cortisol. HSD-1 is expressed in tissues (e.g., liver, adipose, bone, brain, skin, muscle, eye) in which elevated cortisol levels cause morbidity in patients with Cushing syndrome or autonomous cortisol secretion.
- HSD-2 converts cortisol to cortisone in mineralocorticoid-sensitive tissues (e.g., kidney), where it serves a protective function.

Much of the intracellular cortisol that can act on intracellular receptors is made by HSD-1. Cortisol is highly bound by plasma proteins, so only a small fraction is free to enter cells. Cortisone is less protein bound. It enters cells in larger quantities and then converted by HSD-1 to cortisol, which can bind receptors, translocate to the nucleus, and regulate target genes.



- HSD-1 activity is substantially higher in liver than other tissues.
- In liver, cortisol & cortisone are metabolized to tetrahydro metabolites which are rapidly and extensively excreted in urine.
- The metabolite ratio is a sensitive measure of liver HSD-1 activity.
- The urinary ratio cortisone / cortisol is a sensitive measure of kidney HSD-2 activity.
- Both HSD-1 and HSD-2 activity ratios can be measured in spot urine samples.



(Tetrahydrocortisol + Allotetrahydrocortisol) / Tetrahydrocortisone = HSD-1 ratio

CLINICAL TRIAL OF SPI-62, A POTENT HSD-1 INHIBITOR

- Data are from a Phase 1, multiple ascending dose trial conducted by Astellas Pharma of SPI-62, formerly known as ASP3662. (1)
- Subjects received a single dose of placebo or 10 to 50 mg SPI-62 on Day 1, followed by 14 consecutive daily doses of placebo or 10 to 50 mg SPI-62 on Days 5 through 18.
- 48 of 50 healthy adults completed the trial. Two subjects withdrew consent for reasons not related to safety.
- Data were combined across dose groups based on substantial overlap of 95% confidence intervals of urinary HSD-1 ratio distributions:
  - at Baseline, across all dose and ethnicity groups;
  - at Day 18, for change from Baseline across subjects of different ethnicities randomized to placebo; and
  - at Day 18, for change from Baseline across all SPI-62 dose and ethnicity groups.
- ANCOVA models comparing SPI-62 (N = 40) to placebo (N = 10) with covariate adjustment for the baseline, were conducted for statistical inference. Unadjusted data are presented graphically.

ALTERED URINARY GLUCOCORTICOID METABOLITES, BUT NOT CORTISOL, LEVELS

SPI-62 (n = 40), compared to placebo (n = 10), was associated with:

- 45% decrease of tetrahydrocortisol + allotetrahydrocortisol, biomarkers of decreased hepatic intracellular cortisol
- 5-fold increase of tetrahydrocortisone, a biomarker of increased hepatic intracellular cortisone
- 90% decrease of the HSD-1 ratio, which indicates maximal hepatic target inhibition
- No change on the HSD-2 ratio, consistent with expected SPI-62 target specificity
- No change on cortisol, the traditional biomarker of endogenous hypercortisolism
- 2.8-fold increase of total glucocorticoids, an integrative biomarker of cortisol production

HPA AXIS RAPIDLY RESTORES CORTISOL HOMEOSTASIS

SPI-62 (n = 40), compared to placebo (n = 10), was associated with:

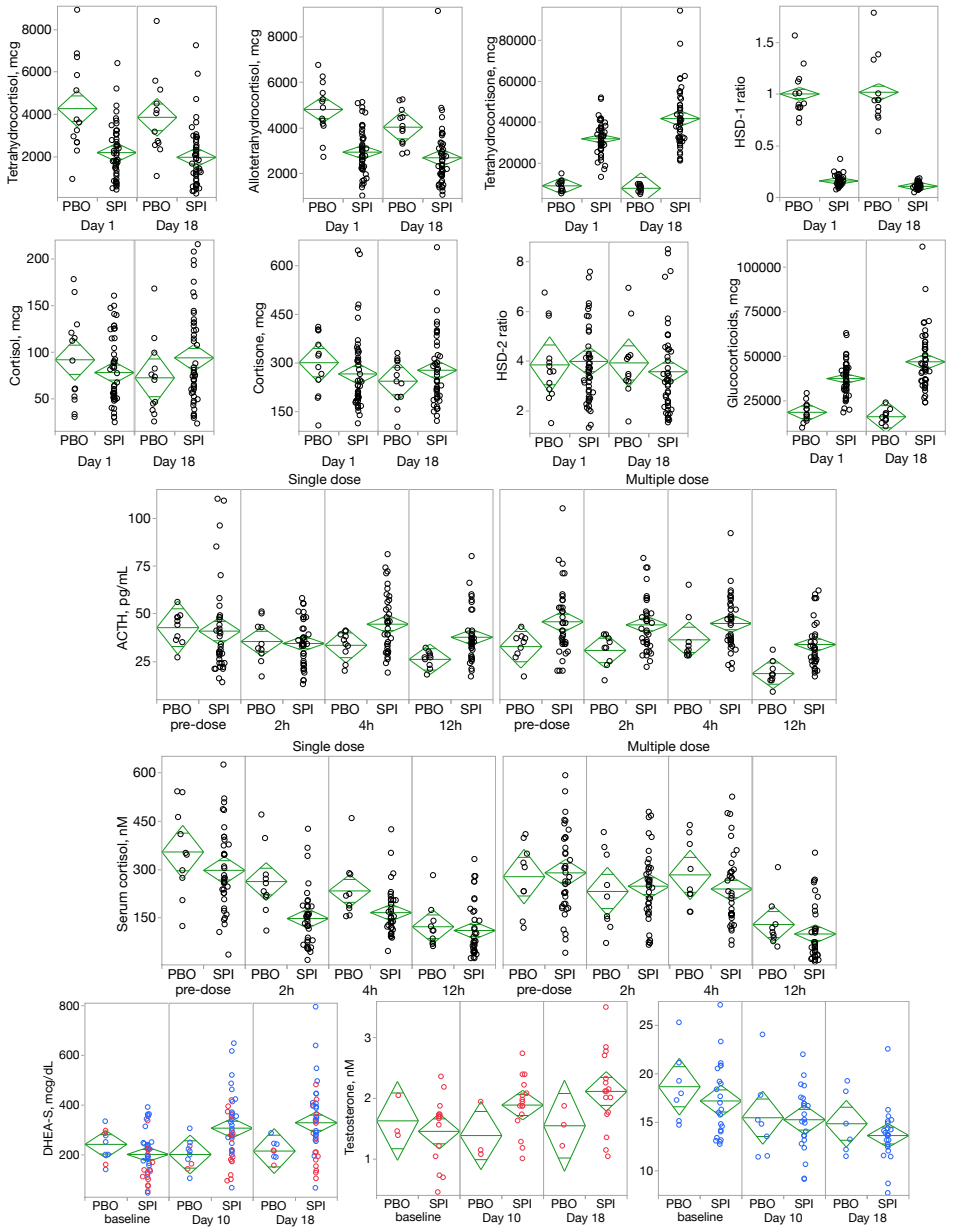
- 33% decrease of serum cortisol at 2 hours after a first SPI-62 dose, but not after multiple doses
- Increased plasma ACTH from 4 hours after a first SPI-62 dose, but not at 2 hours
- No change of serum cortisone or plasma CRH (not shown)

SUBCLINICAL ANDROGEN INCREASES

SPI-62 (n = 40), compared to placebo (n = 10), was associated with:

- 80-90% increase of DHEA-S
- 50% increase of testosterone in female subjects
- No changes of aldosterone, estradiol, FSH, LH, progesterone, or SHBG (not shown)

Only 1 individual testosterone value was above the reference range for females and was not considered clinically significant. No pattern of androgenic adverse events is apparent from 5 completed clinical trials of SPI-62 (n = 177 total, 55 female).



- **Half of hepatocellular cortisol with access to intracellular receptors is generated in healthy adults by HSD-1.**
- **ACTH increase compensates for the effect of HSD-1 inhibition on systemic cortisol levels.**
- **Secondary increases of androgen levels have not been associated to date with clinical consequence.**
- **Large changes of the amount of cortisol that can bind intracellular receptors, and thus cause cortisol-related morbidity, can occur independently of urinary free cortisol levels.**

SPI-62 is now in Phase 2 clinical trials in patients with:

- ACTH-dependent Cushing syndrome (**Poster PMON72**)
- autonomous cortisol secretion (**Poster PSUN20**)

REFERENCE: (1) Clin. Transl. Sci. 2019;12:291-301

Dr. Katz is a shareholder and officer of, and Mr. Mortier is a consultant to, Sparrow. SPI-62 is investigational. This information is not for use in promotion or product commercialization.