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Management Approaches to Congenital Adrenal Hyperplasia in Adolescents and Adults; Latest Therapeutic Developments

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1. Introduction

The main aim of the chapter entitled Management Approaches to Congenital Adrenal Hyperplasia (CAH) in Adolescents and Adults; Latest Therapeutic Developments, will be first to familiarize readers with current treatment guidelines using glucocorticoid and mineralocorticoid replacement in treating this common and under-diagnosed cause of amenorrhea. Next, to introduce readers to the concept of insulin resistance in CAH and treatment approaches based upon increasing insulin sensitivity. Finally, we shall consider possible future directions in the treatment of CAH.

2. Current conventional therapy for congenital adrenal hyperplasia

2.1 Glucocorticoid replacement: Rationale, current dosing considerations and benefits

Conventional therapy for this family of disorders with glucocorticoids and sometimes mineralocorticoid remains, for now, the gold standard. The rationale for this approach is straightforward and logical. CAH is a family of disorders in which there are mutations in one or more genes for enzymes involved in adrenal (and sometimes ovarian) steroidogenesis, rendering the resultant enzyme less functional than the wild type. Alternatively, there is no mutation in the region coding for the enzyme, but one may be found, for example, in the promoter region affecting either gene expression or enzyme activity (Trapp et al., 2011).

In each of these situations the hypothalamic-pituitary-adrenal (HPA) axis goes into overdrive due to negative feed-back attempting to produce adequate levels of cortisol and sometimes aldosterone. When aldosterone synthesis is also impaired the renin-angiotensin aldosterone system (RAAS) likewise goes into overdrive (Merke & Bornstein, 2005; White, 1997).

The presence of partial blocks in the biosynthesis of cortisol and/or aldosterone results in the diversion of a portion of adrenal steroidogenesis into the available unblocked pathway, androgen synthesis. Androgen synthesis is further stimulated by the enhanced activities of the HPA and the RAAS (White, 1997).

For the most part, this strategy of providing the adrenocortical end-products, glucocorticoids and mineralocorticoids, is spectacularly successful. Instituted in the nursery this

therapy will prevent severe salt wasting, dehydration and death in infants born with severe, salt-wasting forms of classical CAH. It prevents most progression of virilization and prepares the infant for corrective external genital surgery, if required. Begun early enough it will usually result in gender identity which is congruent with the child's chromosomal sex (Raff, 2004; Young & Hughes, 1990).

Treatment principles for adolescent and adult patients are quite similar to those used in treating adrenal insufficiency. Total daily maintenance doses of hydrocortisone range from 15 to 30 mg, of cortisone acetate from 12.5 to 37.5 mg and of prednisone from 3 to 5 mg. Dexamethasone is generally avoided because of difficulty of titration at low doses, long half life, resulting in overlap of daily doses, and its lack of any effect on the mineralocorticoid receptor (Speiser et al., 2010; Merke, 2008).

As with adrenal insufficiency, recommended doses for CAH have fallen by 25-35% over the past 10-15 years as better estimates of normal daily cortisol production have become available. With the adoption of lower doses of glucocorticoid it is anticipated that there will be a lower future prevalence of bone loss, hyperglycemia, capillary fragility, and other complications of long term glucocorticoid use (Speiser et al., 2010).

In adrenal insufficiency glucocorticoid is typically dosed in a way that approximates the diurnal rhythm of cortisol secretion e.g. the morning doses of hydrocortisone and cortisone acetate are about twice the evening doses; if prednisone is chosen it is usually dosed in the morning. In CAH the treatment concept is to suppress the diurnal morning surge in adrenal androgen production. Thus, the evening doses of hydrocortisone and cortisone acetate will be double of the morning dose. Prednisone is dosed at bedtime. This dosing schedule is also referred to as reverse circadian dosing. Some workers advocate dosing hydrocortisone and cortisone acetate 3 times a day citing more complete suppression of adrenal androgen synthesis, however, compliance becomes more difficult as the number of daily doses increases (Speiser et al., 2010; Newell-Price et al., 2008).

In patients with classic CAH, hydrocortisone doses may be need to be raised somewhat to suppress progesterone prior to attempting conception, such that a proliferative endometrium may develop, followed by a secretory endometrium in an orderly sequence which will allow implantation to occur. There is no contraindication to breast feeding for women on hydrocortisone or cortisone acetate replacement.

Dexamethasone treatment of mothers to prevent ambiguous external genitalia in the neonate is not recommended outside of well designed IRB-approved clinical trials.

2.2 Mineralocorticoid replacement: Rationale, current dosing considerations and benefits

In patients with severe, salt-wasting forms of classical CAH e.g. salt-wasting 21-hydroxylase deficiency and Visser-Cost syndrome mineralocorticoid replacement is essential in infants and young children as well as most adults. Some older children, adolescents, and adults can manage without supplemental mineralocorticoid if they maintain a high salt intake (Antal & Zhou, 2009). Even in some non-salt wasting forms of CAH there is, at least, mildly impaired aldosterone synthesis. It is recognized that in such patients mineralocorticoid replacement, while not essential for survival, does have a glucocorticoid sparing effect, allowing for maintenance of blood pressure, normal serum electrolytes, and general well being with somewhat lower doses of glucocorticoids, thus reducing the risk for bone loss, hyperglycemia, muscle weakness, and affective disturbances. Normalization of the plasma

renin activity (PRA) may be used as a barometer for adequate mineralocorticoid replacement. Usual adult mineralocorticoid replacement is with fludrocortisones 0.05- 0.15 mg daily.

2.3 Sick day and stress dose adjustments of glucocorticoids and mineralocorticoids

Stress adjustments of glucocorticoids in CAH are similar to those in adrenal insufficiency. Mild stresses such as upper respiratory infections, minor injuries, and minor surgery require a doubling of the dose for 1-3 days. More serious stresses e.g. pneumonia, major fractures, or major surgery will require full stress doses of glucocorticoid e.g. 50-100 mg of hydrocortisone by intravenous piggyback or continuous infusion every 6-8 hours. As with daily maintenance doses of glucocorticoids for adrenal insufficiency, stress glucocorticoid dosage recommendations have fallen for CAH as well. There is now the realization that vascular tone, normalization of serum sodium, and prevention of hypoglycemia in ill and critically CAH patients can be achieved and maintained with significantly lower doses of glucocorticoid then previously prescribed. The current practice reduces the risk of inducing severe hyperglycemia, hypokalemia, and affective changes (Speiser et al., 2010). Intravenous bolus (push) doses of glucocorticoids should be avoided as they have been reported to cause dysrhythmias (Fujimoto et al., 1990).

Mineralocorticoid doses do not generally have to be increased for stress. On mild stress days patients can be instructed to increase their salt and water intake. On severe stress days the use of intravenous 5% dextrose in 0.9 normal saline at about 3 liters/day in combination with high dose hydrocortisone, which has some mineralocorticoid activity at high serum levels, and will bind as an agonist to mineralocorticoid receptors, will provide adequate electrolyte and water homeostasis. Nevertheless, if hyponatremia or hypotension persist, fludrocortisone should be initiated or its dosage should be raised. (Connery & Coursin, 2004; Riepe & Sippell, 2007). Stress glucocorticoid doses should be tapered as rapidly as the patient's precipitating condition allows, monitoring serum glucose and electrolytes as well as blood pressure carefully (Connery & Cousin, 2004).

Clearly, the treatment of the CAHs with glucocorticoids and mineralocorticoids has been one of the outstanding advances in modern medicine. It has been lifesaving for countless infants with classical CAH and has allowed for chromosomally congruent gender identification in many affected patients. It has ameliorated problems such as premature epiphysial closure with reduced adult height, hirsutism, acne, alopecia, menstrual disorders, and hypofertility/infertility. Associated polycystic ovaries often normalize their appearance on ultrasound.

2.4 Limitations of glucocorticoid and mineralocorticoid therapy

In the non-classical CAHs (NCAH), especially those with milder functional abnormalities of the affected enzyme or in some affected heterozygotes, it is often possible to normalize the production of adrenal androgens and steroid intermediates such as 17-hydroxyprogesterone, 17-hydroxypregnenolone, and 11-deoxycortisol with low replacement doses. However, in the more severely affected patients production of androgens and intermediates may remain quite high with symptomatic implications (Merke & Bornstein, 2005).

We are cautioned, appropriately, in these patients not to normalize androgen and intermediate production at the expense of treating with supraphysiologic glucocorticoid doses, which may cause bone loss, hyperglycemia, weight gain, and other more subtle

features of hypercortisolism. We are left, in these patients, to treat the remaining hyperandrogenism with androgen receptor blockers, e.g. spironolactone, which also reduces ovarian/adrenal androgen production (Merke & Bornstein, 2005; Merke, 2008).
Oral contraceptives are frequently prescribed as adjunctive treatment to suppress associated ovarian hyperandrogenism and to impose a regular menstrual cycle (Merke, 2008). Recently, inhibitors of 5α-reductase, finasteride and dutasteride, have been utilized to reduce the conversion of testosterone to dihydrotestosterone, the steroid compound most directly responsible for acne, alopecia, and hirsutism. Of the two medications, dutasteride is the more effective because it inhibits both forms of the enzyme (Choi et al., 2010). Additional strategies include the use of electrolysis for permanent removal of unwanted hair, laser for semi-permanent hair removal, depilatories for temporary hair removal, cosmetic bleaching of hair, benzoyl peroxide and retinoic acid derivatives for acne control and tetracyline, and its derivatives for suppression of *Propionibacterium acnes* in acne.

3. The concept of insulin resistance in congenital adrenal hyperplasia

3.1 Similarities to and overlap with polycystic ovarian syndrome

Clinically, the features of the non-classical adrenal hyperplasias (NCAH's) are:

- premature adrenarche
- menstrual irregularity
- hypofertility/infertility
- acne
- hirsutism
- alopecia
- central adiposity
- acanthosis nigricans
- skin tags
- increased risk of Type 2 diabetes mellitus (T2DM)
- polycystic ovaries

These are nearly identical with those of polycystic ovarian syndrome (PCOS) (Pall et al., 2010). PCOS, which so closely resembles NCAH, is universally recognized to be associated with insulin resistance and is reported to be responsive to the insulin sensitizers metformin (Franks, 2011; Ladson et al., 2011) , troglitazone, rosiglitazone and pioglitazone (Franks, 2011). One report (Paoletti et al., 1996) showed that many patients with PCOS responded to the dopamine receptor agonist, cabergoline, a compound which is now used in the treatment of T2DM. Given the multitude of similarities between PCOS and NCAH it seemed reasonable to believe that NCAH patients, like PCOS patients might be insulin resistant

3.2 Possible mechanisms of insulin resistance in cah

Review of studies linking CAH with insulin resistance and those showing biochemical/phenotypic amelioration with interventions that reduce insulin resistance invites the question - by what mechanism(s) do insulin resistance/hyperinsulinemia affect the expression of CAH?
It is known that many factors affect the expression of both normal and mutant genes-the levels of transcription, translation, and post-translational gene product function. The nuclear transcription factor, peroxisome proliferator-activated receptor gamma (PPAR-γ) affects the

expression of a wide variety of genes. PPAR-γ is found in both the corticotrophs of the anterior pituitary and the adrenal cortex (Mannelli et al., 2010). Short, interfering RNA's (siRNA's) can silence transcription of normal or mutant genes as reported by Inoue et al., 2006.
Hyperinsulinemia increases the biosynthesis of androgen by the adrenal cortex as reported by Arslanian et al (2002). This is partially due to an insulin-induced, post-translational hyperphosphorylation of P450c17α, resulting in an increase in its 17,20 lyase activity in both adrenals and ovaries, thus magnifying the effect of any distal, adrenal steroidogenic defect.
Kelly et al reported that steroidogenic factor-1 (SF-1) activity is upregulated in vitro by insulin in the presence of forskolin (a functional analog of ACTH) in this setting. Increased SF-1 synthesis, as well as increased binding of SF-1 to its response element, resulted in increased transcription of CYP17 causing increased adrenal androgen synthesis in both normal, human adrenocortical tissue and in cultures of the adrenocortical tumor line H-295. In these same two *in vitro* systems insulin inhibited the forskolin stimulated synthesis of the transcription factor *nur77*, an action that results in decreased transcription of CYP21 mRNA, further directing adrenal steroidogenesis toward androgen vs cortisol biosynthesis. Thus, hyperinsulinemia would worsen the phenotypic/biochemical expression of 21-hydroxylase deficiency as well as magnify any other deficiencies of adrenal steroidogenic enzymes (Kelly et al., 2004).

3.3 Review of studies demonstrating insulin resistance in congenital adrenal hyperplasia

3.3.1 Hyperandrogenemia as a general accompaniment of the insulin-resistant state, type 2 diabetes mellitus

Andersson et al. reported that women with T2DM had significantly higher plasma insulin concentrations, lower sex hormone binding globulin (SHBG), and higher circulating free testosterone levels than did BMI and gender matched controls. Men with T2DM had significantly lower total serum testosterone than a matched group of non-diabetic men, but no significant difference in their circulating free testosterone levels. They concluded that women with T2DM were relatively hyperandrogenemic and men with T2DM were normoandrogenic (Andersson et al., 1994).
We noted (Sacerdote et al., 1994, 1995) that both hyperinsulinemia and hyperandrogenemia will suppress SHBG, resulting in lower total serum testosterone in both men and women. We added that other androgens, not measured in their study, e.g. androstenedione and DHEA might be contributing to the lowering of SHBG in both sexes. We reported that all 66 of our consecutive, non-selected, type 2 diabetic patients (60 men and 6 women aged 29-89), had evidence of adrenal hyperandrogenemia as evidenced by elevated basal or cosyntropin-stimulated serum androstenedione, DHEA, DHEA-S, free testosterone, or adrenal steroid intermediates eg 17-hydroxyprogesterone. In our series, the most frequent steroid elevations were of 17-OH-progesterone and 17-OH-pregnenolone, but we also reported glucocorticoid-suppressible elevations of 11-deoxycortisol, and deoxycorticosterone (DOC). In addition, we reported glucocorticoid-reversible depressions of SHBG. Both Andersson's study (Andersson et al., 1994) and ours noted an association between hyperandrogenism and Type 2 DM-an insulin-resistant state.

3.3.2 Non-classical 21-hydroxylase deficiency

Speiser et al. reported insulin resistance in six women with untreated non-classical 21-hydroxylase deficiency using a tolbutamide-modified, frequently-sampled intravenous glucose tolerance test (Speiser et al., 1992). These findings of Speiser's were confirmed in 18

untreated women with non-classical 21-hydroxylase deficiency using the HOMA-IR (Saygili et al., 2005). Singer et al. reported persistence of insulin resistance in a patient with non-classical 21-hydroxylase deficiency after normalization of her serum androgens with glucocorticoid, indicating that the hyperandrogenism was not contributing to the insulin resistance or, alternatively, that any insulin resistance due to hyperandrogenemia was replaced by insulin resistance due to glucocorticoid (Singer et al., 1989). Kroese et al. compared 12 glucocorticoid –treated adult patients with non-classical CAH with 12 controls determining insulin sensitivity by euglycemic clamp and oral glucose tolerance testing. CAH patients were insulin resistant compared with controls. Treatment with pioglitazone 45 mg improved insulin sensitivity and lowered blood pressure in CAH patients (Kroese et al., 2009). In a study of 203 patients with CAH, 199 of whom had 21-hydroxylase deficiency, in the care of specialized endocrine centers across the United Kingdom National Health Service, it was found that 41% were obese and 29% were insulin resistant (Arit et al., 2010). Pall et al. reported that insulin sensitivity in women with non-classical 21-hydroxylase deficiency was indistinguishable from that of lean women with PCOS (Pall et al., 2010). In a meta-analysis it was concluded that NCAH was associated with increased fat mass, BMI, insulin resistance, and the metabolic syndrome (Mooij et al., 2010).

3.3.3 Classical 21-hydroxylase deficiency

Charmandari et al. reported that that, compared to children without classical CAH (n=28), children with classical 21-hydroxylase deficiency (n=16), both salt-wasters (n=12) and those with the simple virilizing phenotype (n=4) had significantly more insulin resistance as assessed by HOMA-IR as well as significantly higher serum leptin levels (Charmandari et al., 2002). Zhang et al. reported that, compared with matched controls, 30 young adult women with classical, simple virilizing 21-hydroxylase deficiency (not on glucocorticoid treatment) had significantly higher BMI, 2-hour post-load plasma glucose, serum triglycerides, fasting insulin, and HOMA-IR as well as lower serum HDL. Serum adiponectin (considered a marker for insulin sensitivity) was markedly lower in the CAH patients. Linear regression analyses revealed that higher serum testosterone concentrations were significantly, positively correlated with metabolic disorder indices and negatively correlated with serum adiponectin concentration (Zhang et al., 2010). Zimmerman et al. studied 27 patients with classical 21-hydroxylase deficiency, aged 4-31 on glucocorticoid replacement and a like number of sex, age, and BMI matched controls. They found that LDL, fasting serum glucose, insulin, and HOMA-IR were significantly higher in the patients with classical 21-hydroxylase deficiency, while HDL was significantly lower. These authors attributed the adverse metabolic changes to glucocorticoid therapy as HOMA-IR showed a significant positive correlation with hydrocortisone dose (Zimmerman et al., 2010). Atabek et al. reported a 5 year old girl with female pseudohermaphroditism due to classical 21-hydroxylase deficiency with insulin resistance and Turner's syndrome. These authors noted an improvement in insulin sensitivity when their patient was treated for hyperandrogenemia with glucocorticoid (Atabek et al., 2005). Ambroziak et al. reported that adult patients with classical 21-hydroxylase deficiency have obesity, hyperinsulinemia, insulin resistance, and hyperleptinemia more frequently than age/sex matched controls (Ambroziak et al., 2010).

3.3.4 Non-classical 3-β-ol dehydrogenase deficiency

Carbunaru et al. have reported that the hormonal phenotype of non-classic 3-β-ol dehydrogenase deficiency in hyperandrogenemic females is associated with insulin-resistant

PCOS and is not a variant of genetic HSD3B2 deficiency (Carbunaru et al., 2004). This article is consistent with a publication by (Lutfallah et al., 2002) that proposed new hormonal criteria for the diagnosis of those patients with mutations in the Type II 3-beta-ol dehydrogenase exon. They noted that in the vast majority of patients who had been diagnosed with non-classic 3-β-ol dehydrogenase deficiency using criteria analogous to those used to diagnose non-classic 21-hydroxylase deficiency no mutation could be found in the HSD3B exon. This, of course, does not exclude the possibility that these patients could harbor mutations in the extra-exonic portions of the gene, for example in the promoter region, as has recently been reported in some patients with 21-hydroxylase deficiency (Araújo et al., 2007). In addition, other factors may affect the transcription, translation, or post-translation activity of steroidogenic genes. For example, insulin up-regulates the transcription of 17-α-hydroxylase and downregulates the transcription of 21-hydroxylase (Kelly et al., 2004), while it also causes a post-translational hyperphosphorylation of P450c17α resulting in a gain of function in its 17,20 lyase activity in both the ovaries and the adrenal cortex which, in turn, magnifies the effects of any distal adrenal steroidogenic enzyme defects and potentiates the effect of LH on ovarian androgen synthesis (Arslanian et al., 2002). Genes with perfectly normal nucleotide sequences may have their transcription blocked by excessive methylation or aberrant histone acetylation.

3.3.5 Other forms of non-classical CAH associated with insulin resistance

Our reports on adrenal hyperandrogenemia and T2DM (Sacerdote et al., 1994, 1995) clearly included patients with 3-β-ol dehydrogenase deficiency and aldosterone synthase deficiency and some who were not definitively characterized, but who had glucocorticoid-suppressible elevations of androstenedione, DHEA, DHEA-S, and free/total serum testosterone as well as glucocrticoid normalizable depressions of SHBG. In Arit's study four of 203 patients with CAH had forms of NCAH other than 21-hydroxylase deficiency (Arit et al., 2010). We studied 26 consecutive, non-selected psychiatric patients taking classical anti-psychotic agents, atypical anti-psychotic agents, and/or valproate and we noted that all 26 had adrenal hyperandrogenemia; 2 had biochemical evidence of 21-hydroxylase deficiency, 8 of 3-β-ol–dehydrogenase deficiency, four of 11-hydroxylase deficiency, and two of aldosterone synthase deficiency (Bahtiyar et al., 2007). All of the above psychotropic agents cause insulin resistance and 10/10 patients who took an insulin sensitizer normalized biochemically.

3.3.6 Studies linking insulin resistance with forms of classical CAH other than 21-hydroxylase deficiency

Charmandari et al.'s series reporting elevated serum leptin levels and insulin resistance in children with classic CAH included 2 patients with 11-hydroxylase deficiency (Charmandari et al., 2002).

4. Studies showing utility of insulin sensitization in adrenal hyperplasia

4.1 Metformin and/or thiazolidinediones in the non-classical adrenal hyperplasias

In 2000 we reported that metformin alone or, in some patients, with the first thiazolidinedione (TZD) troglitazone, normalized elevated serum steroid metabolites and ameliorated acne, alopecia, and hirsutism in patients with T2DM and non-classical forms of 21-hydroxylase deficiency, 11-hydroxylase deficiency, 3-β-ol dehydrogenase deficiency, and aldosterone synthase deficiency (Osehobo et al., 2000). In 2003 we reported that the biochemical /phenotypic expression of NCAH, including 21-hydroxylase deficiency, 3-β-ol dehydrogenase

deficiency, 11-hydroxylase deficiency, and aldosterone synthase deficiency could be normalized with rosiglitazone, an example of which may be seen in (Sacerdote et al., 2003) [Figure 1]. In 2004 we reported that the biochemical/phenotypic expression of NCAH is correctible with pioglitazone (Sacerdote et al., 2004). An example of the combined effect of metformin and pioglitazone as compared with standard treatment in a patient with non-classical 21-hydroxylase deficiency is shown in Figure 2. Note that the suppression of 17-OH-progesterone is more complete with the combined insulin sensitizers and even with metformin

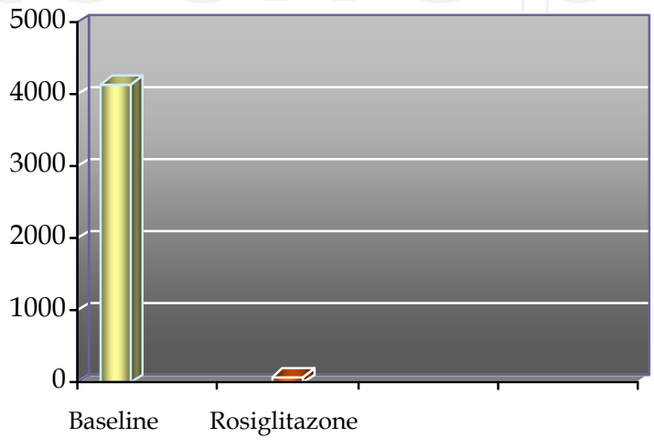

Fig. 1. Response of a 43-year-old Male's 17-OHP (ng/dl) to rosiglitazone 4mg twice daily.

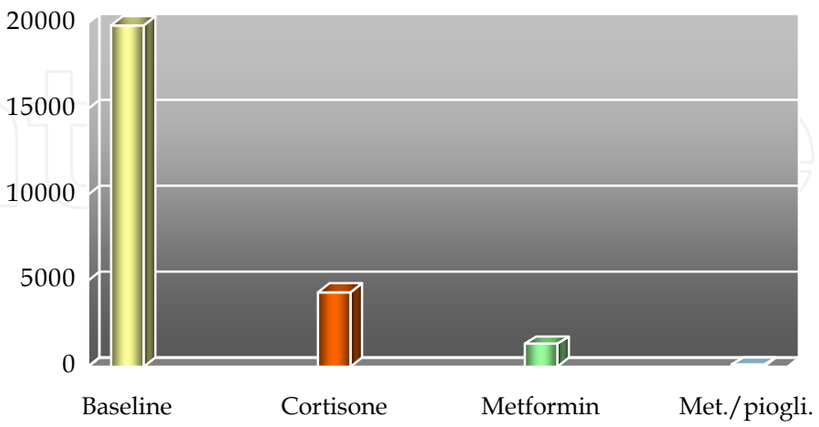

Fig. 2. Response of a 57-year-old Female's 17-OHP (ng/dl) to cortisone acetate, metformin, & pioglitazone

monotherapy than it is with standard treatment. Arslanian et al. reported that metformin treatment in obese teens with PCOS and impaired glucose tolerance (IGT) ameliorated their exaggerated adrenal response to ACTH with concomitant reduction in insulinemia/insulin resistance (Arslanian et al., 2002). The time course of biochemical improvement in NCAH patients treated with metformin or a TZD is quite rapid-within 24 hours of initiating therapy.

4.1.2 Metformin or rosiglitazone in the psychotropic/valproate-induced adrenal hyperplasias

Many medications exert an endocrine disrupter effect by virtue of directly causing insulin resistance or indirectly causing insulin resistance by increasing appetite with resultant weight gain. Among these are both classical and atypical anti-psychotic drugs, valproate, which has also been associated with PCOS (Bilo & Meo, 2008), nucleoside analogs, and protease inhibitors. The latter two groups of anti-retroviral drugs have also been associated with adrenal hyperplasia (Sacerdote, 2006). In our study we found that metformin corrected adrenal hyperandrogenism in 8/8 patients and rosiglitazone corrected adrenal hyperandrogenism in 2/2 patients on anti-psychotic drugs and/or valproate (Bahtiyar, 2007). (Figures 3 and 4).

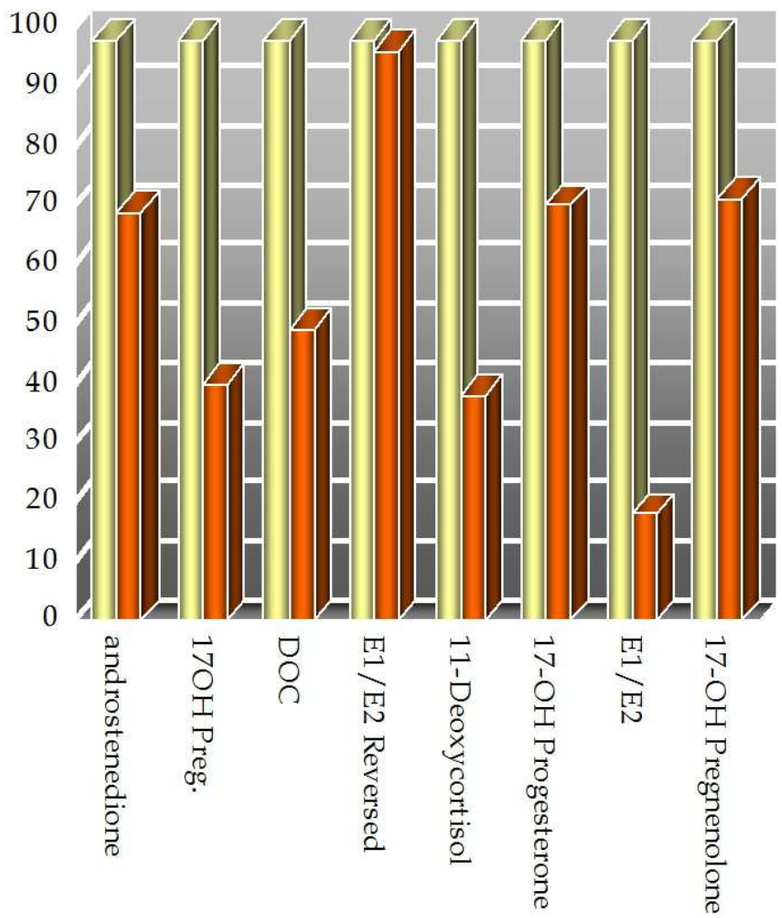

Fig. 3. Effect of metformin on elevated steroid metabolites (Represented a % of baseline). lightly shaded bars are baselines; darkly shaded bars are on metformin treatment.

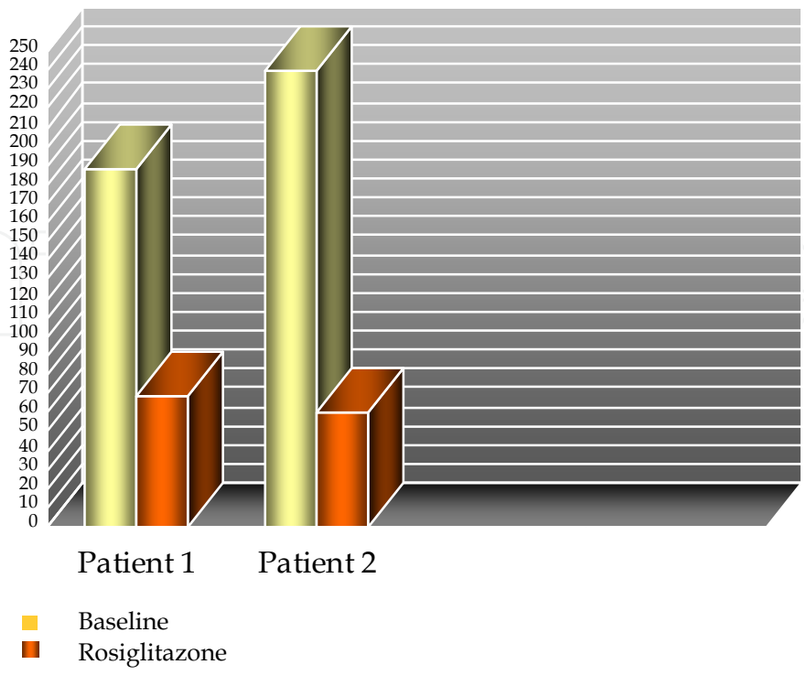

Fig. 4. Effect of rosiglitazone on elevated baseline 11-deoxycortisol level (mg/dl)

4.1.3 Metformin to treat classical 21-hydroxylase deficiency

Because the classical CAH's are much less common than the non-classical forms and also because we are adult endocrinologists and many adolescent/adult classical CAH patients tend to remain in the care of their pediatric endocrinologists, it was a number of years from when we first conceived the notion of treating classical CAH with insulin sensitizers until we were able to participate in the treatment of a classical CAH patient through the collaboration of a pediatric endocrine colleague, Dr. Levon Agdere (Mapas-Dimaya et al, 2008). Our patient was a 17-year-old female who was born with ambiguous genitalia and developed severe hyponatremia and dehydration in the nursery, where she was correctly diagnosed and appropriately treated. At one year of age she underwent clitoroplasty. During 4 years of treatment with her previous pediatric endocrinologist her vital signs and electrolytes remained normal and her height was 142.33 cm which was below the third percentile for her age. A bone age performed at 15.5 years was slightly advanced at 16.0 years. Since age 13 she had been on hydrocortisone 30 mg/day given in two divided reverse circadian doses (10 mg in am and 20 mg in pm) as well as fludrocortisones 0.05 mg daily. Medication compliance was verified with pill counts and refill data. On this regimen she continued to have normal serum electrolytes, glucose, blood pressure, and external genitals, but she noted truncal obesity, hirsutism, acanthosis nigricans, and amenorrhea. Her 17-OH-progesterone remained persistently elevated at 3410 ng/dl (20-500) as was her serum total testosterone at 326 ng/dl (15-70). She was maintained on her glucocorticoid/ mineralocorticoid regime and after obtaining the informed consent of the patient and her parents metformin 500 mg orally after breakfast and supper was added. As seen in Figures 5 and 6 both steroid metabolites fell by about 50% on this combined regimen to 1539 ng/dl and 163 ng/dl respectively. Her amenorrhea resolved and her

hirsutism improved. Our long term intention was to gradually up-titrate her metformin dose and, if necessary, add a TZD until levels of both steroid metabolites normalized and then begin a cautious tapering of her glucocorticoid dosage, however, our patient declared herself satisfied with her initial improvement and declined to undergo further adjustments in her treatment or further testing.

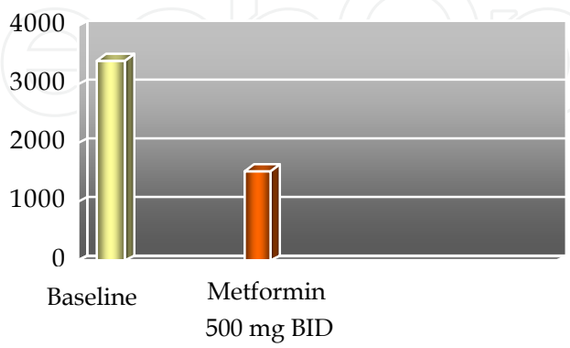

Fig. 5. Effect of metformin addition on 17-OHP (ng/dl) in a patient with classical, salt-wasting 21-hydroxylase deficiency

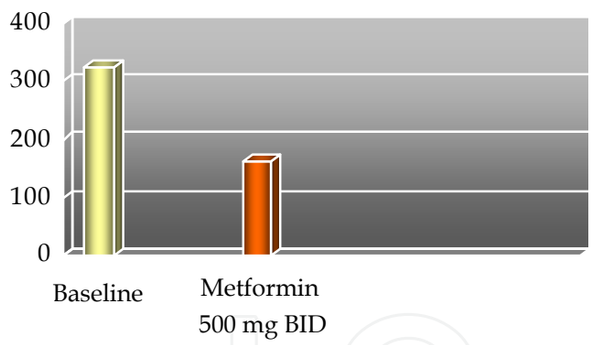

Fig. 6. Effect of metformin on serum total testosterone (ng/dl) in classical 21-hydroxylase deficiency

4.1.4 Limitations of metformin and thiazolidinediones in the treatment of CAH

Although metformin has been shown to be effective as monotherapy or with a TZD for several forms of NCAH and as an adjunctive therapy for classical, salt-losing 21-hydroxylase deficiency, it is currently unknown whether metformin would be an effective treatment for classical, simple virilizing 21-hydroxylase deficiency or for any other form of classical CAH. We do not know if metformin monotherapy or combination therapy with a TZD could ultimately replace glucocorticoid completely in any of the classical CAH's.

In women with PCOS, metformin has been shown, not only to be safe to use throughout pregnancy, but to reduce hyperinsulinemia, weight gain, gestational diabetes mellitus (GDM), and spontaneous abortion (Glueck et al., 2004; Jakubowicz et al., 2002). Metformin is generally

considered safe in both gestational and pre-gestational diabetes mellitus and GDM as it is U.S. F.D.A. Class B. There is also evidence that is safe in nursing mothers (Feig et al., 2007).

Many patients are unable to tolerate the gastrointestinal side effects of metformin, particularly at maximally effective doses. The tolerability of metformin may be increased by a number of different strategies:

- Administration after meals
- Gradual dose titration to allow for adaptation to the drug
- Use of extended release preparations which are better tolerated than the short acting tablets
- Use of liquid preparations (Riomet^{R})
- Use of extended release polymer form (Glumetza^{R})
- Addition of an H_2 blocker or proton pump inhibitor

Metformin should be avoided or very closely monitored in patients with Stage III or worse chronic kidney disease, patients with serious bacterial infections, and for at least two days before and after administration of iodinated intravenous radiographic contrast materials or before and after major surgery, so as not to increase the risk of lactic acidosis. There is little risk of serious hypoglycemia with metformin monotherapy, but mild hypoglycemia may occur if meals are skipped, skimped, or delayed. Serum vitamin B12 and folate levels should be checked periodically in patients using metformin as deficiencies may develop resulting in elevated serum homocysteine levels and peripheral neuropathy, especially in patients with comorbid diabetes.

TZD's have been shown to ameliorate the biochemical/phenotypic findings in most forms of NCAH. To date there are no studies or case reports where they have been used to treat classic CAH. Common side effects of this class of drugs include weight gain, increased subcutaneous fat mass, and edema. Less common, but more serious adverse effects of this class include: congestive heart failure, bone loss, fracture, and bladder carcinoma. With regard to the latter, we have unpublished data in one diabetic patient suggesting reversibility of pre-macroscopic bladder carcinoma after withdrawal of TZD's.

TZD-mediated edema appears to respond well to thiazides, spironolactone, triamterene, and, in our experience, to the renin antagonist aliskerin. It is somewhat resistant to loop diuretics such as furosemide. Data from the PROactive study (Dormandy J et al, 2009) indicate that congestive heart failure developing in patients taking TZD's is no more treatment refractory or lethal than that occurring in Type 2 diabetic patients not using TZD's.

To date there are no randomized control trials (RCT's) on treatment or prevention of TZD-associated bone loss, although in the authors' experience osteopenic/osteoporotic TZD users respond satisfactorily to standard treatments.

The use of rosiglitazone in the treatment of T2DM has been questioned as a result of a meta-analysis published by Nissen and Wolski (Nissen & Wolski, 2007) reporting a "signal" of increased risk of myocardial infarction in rosiglitazone users compared to Type 2 diabetics not using this drug. This report, while controversial, has resulted in rosiglitazone being banned in the EU and severely restricted in the US.

Although many women have become pregnant while taking TZD's either for T2DM or for PCOS and there have not been reports of an adverse effect upon the pregnancies, there have been no published reports of their use beyond the first trimester. It is recommended that TZD's be stopped when pregnancy is suspected or confirmed. TZD monotherapy does not result in hypoglycemia.

5. Utility of lifestyle interventions in the treatment of non-classic aldosterone synthase deficiency

We first reported the non-classic form of aldosterone synthase deficiency in 1999 (Osehobo & Sacerdote, 1999). Before this only the rare, severe salt-wasting form of this disorder (Visser-Cost syndrome) was known. Subsequently we reported that the biochemical/phenotypic expression of non-classic aldosterone synthase deficiency could be normalized by weight loss and exercise, two interventions that reduce insulin resistance in two women with this disorder (Sacerdote, 2002). (Figure 7).

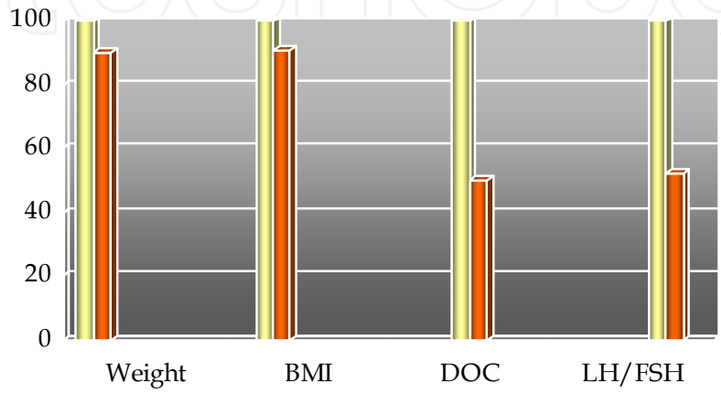

Fig. 7. Percent changes with weight loss and exercise in two women with non-classic aldosterone synthase deficiency. Light bars are baselines, shaded bars are post-treatment

6. Utility of gastric bypass surgery in the treatment of non-classical 11-hydroxylase deficiency

Recently we found that a patient of ours with non-classical 11-hydroxylase deficiency, T2DM, and morbid obesity who underwent Roux en Y gastric bypass surgery normalized her serum 11-deoxycortisol as effectively with surgery as she previously had done with metformin plus pioglitazone (Figure 8). Roux-en-Y gastric bypass has previously been reported to ameliorate PCOS (Eid et al., 2005).

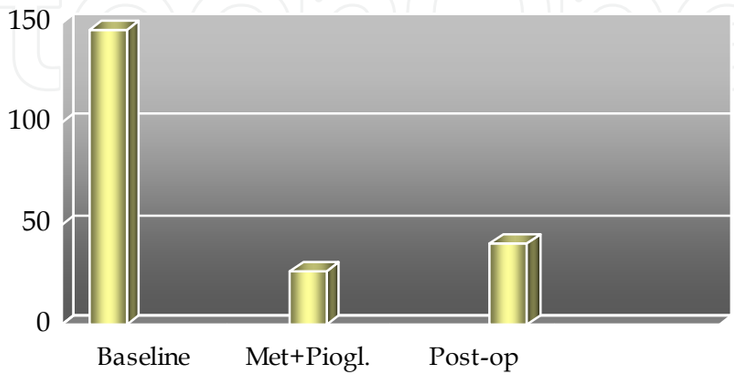

Fig. 8. Response of Patient's 11-deoxycortisol (ng/dl) to Roux-en-Y Gastric Bypass. (Normal < 51)

7. Future directions

7.1 Large randomized control trials of metformin/thiazolidinediones in classical CAH

While the therapeutic efficacy of metformin and TZD's in NCAH is fairly well established, we only have a single case report of metformin being used in classical CAH. We do not know whether metformin and/or TZD's can completely normalize serum levels of 17-hydroxyprogesterone and testosterone when added to steroid "replacement" , nor is it yet known whether metformin/TZD could actually render steroid replacement unnecessary in treating classical salt-wasting 21-hydroxylase deficiency. We have no data as to whether these insulin sensitizers have any efficacy in the treatment of any other form of classical CAH. Well designed RCT's will be necessary to answer these important questions.

7.2 Other insulin sensitizers in congenital adrenal hyperplasia

7.2.1 Dopamine agonist pilot studies

Increasing dopaminergic tone has been reported to have an insulin sensitizing effect (Pijl et al., 2000; Scranton R et al., 2010) and dopamine receptor agonists e.g. bromocriptine are approved for the treatment of T2DM and PCOS, while dopamine receptor antagonists are known to be associated with insulin` resistance and increase the risk for development of glucose intolerance. Cabergoline is used successfully in treating PCOS (Paoletti et al., 1996) as is bromocriptine (Spruce et al., 1984). On this basis we might predict that CAH might improve if treated with dopamine agonists.

7.2.2 Vitamin D pilot studies

Studies in animals show that vitamin D deficiency is associated with impaired insulin sensitivity, and that insulin secretion can be increased by vitamin D supplementation (Tai et al., 2008). Epidemiological studies in man show associations between low vitamin D levels and glucose intolerance (Nunlee et al., 2011). Pittas et al. systematically reviewed the intervention trial evidence for the role of vitamin D and/or calcium in the prevention of metabolic syndrome and T2DM (Pittas et al., 2007). On the basis of evidence from small intervention trials or post hoc analyses of trials, they concluded that it was difficult to be definite whether or not vitamin D and/or calcium were important in the prevention of T2DM, and that effects might only be manifest in people who were particularly at risk of T2DM. Other authors have implicated Vitamin D deficiency/insufficiency in the pathogenesis of insulin resistance, pre-diabetes, T2DM, and PCOS (Cavalier et al., 2011; Wehr et al., 2011). Rashidi et al reported that supplementation of just 400 IU daily of Vitamin D increased the ovulation rate significantly when added to 1500 mg/day of metformin (Rashidi et al., 2009). We have just begun to collect Vitamin D data on some of our NCAH patients and the first three have 25-OH-Vitamin D levels ranging from 18-19 ng /dl. These include one patient with 21-hydroxylase deficiency, 1 with p450-oxidoreductase deficiency, and one male patient with glucocorticoid-suppressible elevated DHEA-S. Given this data it may be reasonable to embark on pilot studies utilizing Vitamin D as monotherapy or in combination with other agents in the treatment of NCAH.

7.2.3 Bile acid binding pilot studies

The bile acid binding resin, colesevelam, has recently been approved for the treatment of T2DM in addition to its original indication for the treatment of hypercholesterolemia. It improves insulin resistance in a diet-induced rodent model by increasing the release of GLP-

1 (Zhang et al., 2010). In a pilot study Schwartz et al. reported that in patients with T2DM colesevelam had no effect on peripheral insulin sensitivity or glucose absorption, but may improve glycemic control by improving whole body insulin sensitivity. Pilot studies with this agent in both PCOS and NCAH might be warranted due to its insulin sensitizing effects (Schwartz et al., 2010).

7.2.4 GLP-1 agonist pilot studies

The GLP-1 agonists exenatide and liraglutide are both associated with weight loss, the latter somewhat more so. The weight loss, particularly that of visceral and non-adipose tissue fat, is associated with an improvement in insulin sensitivity (Liu et al., 2010; Defronzo et al., 2010). Exenatide has been reported to ameliorate PCOS (Elkind-Hirsch et al., 2008). Therefore, it seems reasonable to plan pilot studies with these agents in CAH.

7.2.5 Orlistat pilot studies

The fat absorption blocking agent orlistat is approved as a weight loss aid when combined with diet and exercise in the U.S. in both a 60 gm over the counter form and a prescription only 120 mg form. In Canada it is approved for the treatment of T2DM. Panidis et al. reported that orlistat in combination with diet produced significant weight loss and improvement in insulin sensitivity in obese women, with or without PCOS. In addition, serum testosterone levels were significantly improved in women with PCOS (Panidis et al., 2008). Based on these data pilot studies of orlistat in NCAH should be performed.

7.2.6 Cannabinoid receptor blockade pilot studies

Stimulation of the CB-1 cannabinoid receptor has known orexic and euphoric effects, while its blockade with rimonabant has been associated with anorexic and dysphoric effects and results in weight loss, reduced insulin resistance, and improvements in glycemia and serum lipid levels (Migrenne et al., 2009) and has shown efficacy in PCOS patients (Sathyapalan et al., 2008). Rimonabant was not approved in the U.S. and its approval was withdrawn in Europe because of a higher suicide risk due, presumably, to its dysphoric effect. The risk/benefit ratio of this class of agents might be improved by better patient selection, selective co-administration of an anti-depressant, treatment of hyperhomocysteinemia (which may play a role in depression, or the development of selective cannabinoid receptor modulators, possessing the beneficial anorexic effect of the class without causing dysphoria. The selective estrogen receptor modulators (SERM's), now in widespread clinical use, provide a model for such future development. Since these agents reduce insulin resistance, we might predict that they could ameliorate CAH.

7.2.7 Continuous positive airway pressure (CPAP) in CAH patients with obstructive sleep apnea (OSA)

Many, if not most, insulin resistant people have OSA (Vgontzas et al., 2005). Treatment with CPAP has been shown to improve insulin sensitivity in women with PCOS (Tasali et al., 2011). Vgontzas et al have reported that the inflammatory cytokines, TNF-α and IL-6 are elevated in patients with OSA, independently of obesity and that visceral fat was the primary parameter linked with OSA (Vgontzas et al., 2005). The fact that they found that OSA was more common in women with PCOS suggested a pathogenetic role of insulin resistance in OSA. The beneficial effect of a cytokine antagonist on excessive daytime

sleepiness in obese, male apneics and on sleep disordered breathing in a general, random sample supports the hypothesis that cytokines and associated insulin resistance are mediators of excessive daytime sleepiness and OSA. Hamada et al have reported that with nasal CPAP in a CAH patient with OSA they were able to reduce the maintenance glucocorticoid dosage (Hamada et al., **2011**). CAH patients who have clinical features consistent with OSA, might benefit from undergoing a sleep study followed by a CPAP titration study if the initial sleep study is diagnostic. Alternatively, inhibitors of TNF-α and IL-6 might be useful adjuncts in the treatment of CAH.

7.2.8 Curcumin

Curcumin is a component of the popular spice, turmeric. It has been reported to decrease levels of the inflammatory cytokine, TNF-α, which, in turn, downregulates the transcription factor PPAR-γ. Administration of curcumin results in up-regulation of PPAR-γ m-RNA and protein, which we would predict would improve insulin sensitivity (Gosh et al., 2009). Pilot studies with curcumin in CAH patients, would, therefore, be of interest given the absence of any known adverse effects. Other spices, herbs, and supplements known or suspected to have insulin sensitizing effects would also be worth exploring in CAH.

7.2.9 L-carnitine

L-carnitine has been reported to reduce insulin resistance, when added to orlistat, significantly more than orlistat alone (Derosa et al., 2010). For this reason, a pilot study treating CAH patients with this supplement would be of value.

7.3 Other insulin-lowering agents

7.3.1 Somatostatin analogs

Somatostatin and its analogs- octreotide, octreotide LAR, and lanreotide partially suppress insulin secretion; reduction of hyperinsulinemia by this means could result in amelioration of both PCOS and CAH. Gambineri's group reported that octreotide-LAR improved the ovulation rate and hirsutism and showed nearly significant trends toward greater reductions in serum testosterone and androstenedione compared with placebo in dieting women with abdominal obesity and PCOS (Gambineri et al., 2005). Pilot studies of these drugs in these two conditions, would, therefore, be of interest. Because they reduce the secretion of growth hormone they would not be suitable for use in children or adolescents.

7.3.2 Diazoxide and phenytoin

These drugs both decrease insulin secretion and have been reported to be helpful in treating some PCOS patients (Bercovici et al., 1996; Verrotti et al., 2011). On this basis we might predict a response in CAH patients as well. In designing pilot studies with these agents patients with pre-diabetes or low bone density should probably be excluded due to the diabetogenic potential of both drugs and the accelerated Vitamin D clearance attributed to the latter.

7.4 Gene therapy

Gene therapy, wherein the defective gene is supplemented with a functional one should, theoretically, be the ideal therapy for every form of CAH, with the possible exception of non-classical 3-β-ol dehydrogenase deficiency, for which no mutation in the exon has been identified (Carbunaru et al., 2004).

7.4.1 Adenoviruses

Adenoviruses are adrenocorticotropic, making them a good vector in which to deliver functional genes. 21-hydroxylase genes have been delivered in adenoviruses by intra-adrenal injection in 21-hydroxylase-deficient mice and bovine adrenocortical cells have shown functional and morphological changes in the adrenal cortices after transfection with recombinant adenovirus (Loechner et al., 2010). While encouraging, overall safety and specificity in targeting the adrenal cortex remains to be established. There may be a need to develop new vectors (viral or non-viral) to optimize the specificity and efficiency of adrenal gene transfer and ensure long term DNA integration. Recently, other recombinant viruses, e.g. retrovirus, lentivirus, adeno-associated virus, and Herpes simplex have been successfully used as gene vectors. Non-viral gene delivery methods that use natural or synthetic compounds or physical forces to deliver DNA to the cell are now available.

7.4.2 Adult stem cells

Adult stem cells may be obtained from a variety of tissues and have been studied in several milieus, especially the hematopoietic system. Limiting factors with adult stem cells include:

- Limited pluripotency
- Difficulty of maintenance in vitro
- HLA compatibility restraints on transplantation, thus requiring immunosuppression with its attendant risks, cost, and inconvenience

Recent studies have described methods which are generally applicable for the preparation of induced pluripotent stem cells (IPSC's) from various somatic cell lineages. Marrow-derived mesenchymal cells (MSC's) are unique in that they are obtained from adults, yet are still pluripotent. MSC's or IPSC's obtained from CAH patients would harbor a genetic defect in steroidogenesis and, thus, would only be helpful as cellular vectors for gene therapy. Despite their shortcomings, the use of adult stem cells benefits from a longer investigational track record and avoids ongoing political issues with the use of fetal stem cells. Yazawa et al. have reported that human MSC's transfected with SF-1, a transcription factor required for both adrenal and gonadal steroidogenesis, differentiate into cortisol producing cells rather than androgen producing cells when transplanted into mouse testis, while Gondo et al reported that such cells were ACTH-responsive (Yazawa et al., 2006; Gondo et al., 2004). Another approach is that of Hammer et al who characterized a subpopulation of adrenal cells that are typically dormant or undifferentiated. Stimulation of these cells to differentiate into mature adrenal cells is possible and studies aimed at collecting this quiescent population for differentiation/regeneration of adrenal tissue could be helpful in both CAH and adrenal insufficiency (Kim et al., 2007).

7.4.3 Embryonic stem cells

Embryonic stem cells (ESC's) offer an approach that avoids many of the problems inherent with the use of adult stem cells. ESC's harvested during the blastocyst stage are easier to culture *in vitro* and remain for longer periods in the pluripotent stage. ESC's could be triggered to differentiate into regulated, steroidogenic cells using methodologies derived from adult stem cell studies. As with adult tissue transplants, HLA matching is needed and there is the potential for graft rejection and, therefore, the necessity of using immunosuppressive

therapy. The next generation of ESC's could be so closely matched that post-transplantation immunosuppressive treatment would not be needed (Loechner et al., 2010).

7.5 Corticotropin releasing hormone (CRH) antagonists

Inhibition of CRH should dampen the secretion of ACTH, which should facilitate the normalization of adrenal androgen secretion with lower doses of glucocorticoid. Pre-clinical studies with the CRH antagonist alarmin demonstrated blockage of CRH-1 receptor-induced increases, both in adrenal size and behavioral responses. CRH analogs with more extended action e.g. astressin inhibit ACTH release. CRH 9-41 reduces stress measures in sheep. Human CRH receptor antagonist trials demonstrated a reduction in CRH-associated signs of anxiety and depression. Since these studies have not unequivocally demonstrated reductions in CRH-induced ACTH secretion or an effect on cortisol secretion, their clinical relevance remains uncertain at present (Loechner et al., 2010).

7.6 Inhibition of ACTH secretion/action

The discovery of selective melanocortin receptor subtypes, eg MC2-R, for ACTH in the adrenal cortex affords the possibility of inhibition of ACTH action in the adrenal cortex with a diminution in adrenal androgen production. This approach could have a glucocorticoid sparing effect. Clinical trials will be important to assess the resilience of HPA reserve and the safety of this approach.

Blockade of ACTH secretion is under investigation. *In vitro* studies showed that ACTH release from corticotrophs is coupled with the dihydropyridine-sensitive subclass of voltage-dependent calcium channels Clinical trials in Cushing disease reported acute decreases in ACTH levels with calcium channel blockers such as nifedipine and amlodipine. A small trial reported similar magnitude plasma ACTH reductions in 13 children with either classic salt-wasting or simple, virilizing 21-hydroxylase deficiency.

Other agents which may decrease ACTH secretion include the serotonin receptor blocker, cyproheptadine, the dopamine receptor agonist, cabergoline, and the GABA receptor inhibitor, valproate. These agents have been reported to be efficacious in both Cushing disease and Nelson's syndrome, and for this reason, may prove to be helpful in CAH (Loechner et al., 2010).

7.7 Newer glucocorticoid delivery strategies

Studies of circadian cortisol delivery using either hydrocortisone infusions or modified release oral formulations demonstrate that these systems can better mimic physiologic cortisol rhythm, resulting in better glucocorticoid replacement and ACTH suppression in CAH patients. Continuous subcutaneous cortisol infusion (CSCI) has proven effective and well tolerated for over 4 years in a 14 year old CAH patient and resulted in a 50% reduction in daily cortisol dosage within the first 3 months of treatment (Loechner et al., 2010). Two glucocorticoid formulations that exploit the pharmacokinetic peak of once/day, dual-timed cortisol to mimic the diurnal variation peak of ACTH, facilitating more physiologic delivery of cortisol are currently being evaluated. *Chronocort*, one such preparation, seems promising. In a head to head study with *Cortef* dosed 3 times/day with a larger evening dose, it was reported that the *Cortef* regimen resulted in 3 distinct peaks, while a single daily peak at 0600 was noted with bedtime dosing of *Chronocort*. At 0600 levels of 17-OH-progesterone, ACTH, and androstenedione were lower with *Chronocort*, however, afternoon androgen control was better with *Cortef*.

7.8 Aromatase inhibitors

These agents will help block the conversion of androgens to estrogens and thus help block premature epiphysial closure in children and adolescents with CAH (Loechner et al., 2010).

7.9 GnRH agonists with or without growth hormone

As with central precocious puberty, GnRH agonist monotherapy or in combination with GH has been reported to improve the chances of reaching predicted adult height (PAH) in CAH patients with early puberty due to early maturation of the hypothalamic-pituitary-gonadal (HPG) axis. While GnRH agonists prevent premature epiphyseal closure, GH can prevent the stalling in vertical growth velocity that occurs otherwise when precocious puberty is either prevented or aborted (Loechner et al., 2010).

8. Summary/conclusions

In summary, a role for insulin resistance in the pathogenesis of NCAH may be suspected because of numerous similarities in the clinical expression of PCOS and NCAH.
Confirmation of the presence of insulin resistance in CAH has been reported for:

- Non-classical 21-hydroxylase deficiency
- Non-classical 3-β-ol dehydrogenase deficiency
- Non-classical 11-hydroxylase deficiency
- Classical simple virilizing 21-hydroxylase deficiency
- Classical salt-wasting 21-hydroxylase deficiency
- Classical 11-hydroxylase deficiency

Metformin, troglitazone, rosiglitazone, and pioglitazone-all agents known to reduce insulin resistance and ameliorate PCOS have been shown to phenotypically/biochemically ameliorate:

- Non-classical 21-hydroxylase deficiency
- Non-classical 3-β-ol dehydrogenase deficiency
- Non-classical 11-hydroxylase deficiency
- Non-classical aldosterone synthase deficiency
- Classical salt-wasting 21-hydroxylase deficiency

Weight loss by lifestyle modification (diet + exercise) has been shown to normalize DOC levels, the LH/FSH ratio and phenotypically ameliorate non-classical aldosterone synthase deficiency. Roux-en-Y gastric bypass has been shown to phenotypically/biochemically ameliorate non-classical 11-hydroxylase deficiency.
ALL INSULIN SENSITIZING INTERVENTIONS THUS FAR INVESTIGATED AMELIORATE EVERY FORM OF CAH TESTED TO DATE.

- While glucocorticoid/mineralocorticoid replacement/suppression has been spectacularly successful in the treatment of CAH and remains, for now, the gold standard for therapy of this family of disorders, there remain many patients for whom the goal of adequate androgen suppression, while avoiding the pitfalls of hypercortisolemia, remain elusive. Androgen receptor or 5-α-reductase blockade may be added to blunt the clinical effects of inadequately suppressed adrenal androgen secretion. In the future glucocorticoid/ mineralocorticoid therapy may be further refined by the use of novel long acting and dual peak preparations of hydrocortisone and newer steroid delivery systems e.g. CSCI. Adrenal androgen secretion may be

further reduced in the future by means of CRH or ACTH blockade, while the combination of GnRH agonists with GH may help to more nearly achieve PAH.

- The recognition that insulin resistance/hyperinsulinemia is a regular feature in CAH that contributes to its biochemical/phenotypic expression has led to the finding that metformin and/or TZD's may replace standard therapy in NCAH and that metformin may be used, at least as adjunctive therapy, in classic, salt-wasting 21-hydroxylase deficiency. Exercise and weight loss have been shown to ameliorate non-classic aldosterone synthase deficiency, while Roux-en-Y gastric bypass can normalize the biochemical expression of non-classic 11-hydroxylase deficiency. Other therapies that decrease insulin levels, including those that have already shown efficacy in PCOS, seem likely to show therapeutic benefit in CAH.
- In the future it is likely that there will be further refinements in steroid replacement/suppression, more widespread use of treatments to decrease hyperinsulinemia, and further progress in gene therapy.

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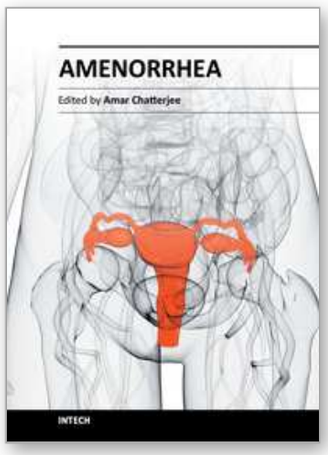

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