Pharmacology Biochemistry & Behavior, Vol. 17, pp. 1225–1231, 1982. Printed in the U.S.A.

Prednisolone Effects upon Body and Organ Weights, Water Intake, and Several Behaviors

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Received 7 May 1982

SEWELL, R. G., J. A. GALLUS AND K. P. NANRY. *Prednisolone effects upon body and organ weights, water intake, and several behaviors.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1225–1231, 1982.—Various behavioral sequelae have been noted in patients receiving prolonged, high-dose glucocorticoid therapy. The present study assayed several behavioral dimensions of rats receiving daily intramuscular injections of the synthetic glucocorticoid, prednisolone. Specifically, assessments of water intake, nocioception, locomotion, and the grasping responses were conducted; measures of gonadal, adrenal, and total body weights were also taken. Twelve daily injections were given to four groups (N=6/group) of immature male rats with each group receiving a different dose of drug (0.0, 8.0, 16.0, 32.0 mg/kg). Prednisolone generally suppressed home-cage water intake, and latencies to hind paw-lick in the hot-plate assay. Measures of wheel running and the grasping response were generally enhanced. Absolute gonadal and adrenal weights as well as total body weights were decreased. Relative organ weights suggested that daily prednisolone treatments had produced suppression of the pituitary-adrenal axis. It was concluded that prednisolone is active in these assays and that such measures may be useful in studies of drug interaction with this agent.

Prednisolone Behavioral side-effects Gonads Pituitary-adrenal axis Water intake Body weight
Hot-plate test Grasping response Cancer chemotherapy Glucocorticoids Nocioception Locomotion

PREDNISOLONE and other synthetic glucocorticoids are employed at high doses and for prolonged periods in the treatment of acute lymphocytic leukemia, lymphomas, certain carcinomas of the breast, and miscellaneous solid tumors [15,26]. However, patients receiving chemotherapy combinations which include glucocorticoids have experienced high rates of behavioral abnormalities [38,46]. Various evidence suggests that high levels of circulating glucocorticoids, whether caused by endogenous or iatrogenic factors, predispose patients to psychiatric complications [15, 24, 25, 33, 45, 50]. It is thus plausible that glucocorticoids contribute substantially to the high incidence of behavioral abnormalities in chemotherapy recipients.

In glucocorticoid-treated patients, a large variety of behavioral disorders have been observed. Marked alterations have been reported in consummatory behavior [49], motor activity [47], weight [18], sleep [15], and affect [25], among others. Prolonged glucocorticoid therapy may impair functioning of the pituitary-adrenal axis through negative feedback mechanisms [15,18], induce a characteristic "steroid myopathy" with associated weakness and fatigability [37], and alter various aspects of the sensorium [15]. Further, such behavioral dysfunctions appear protean, thus resulting in increased difficulties of diagnosis [15].

At present, which individuals will display behavioral sequelae, as well as which reactions will manifest, remain unpredictable [25]. This lack of predictability may relate to the large number of factors simultaneously acting upon the chronically ill patient. Such glucocorticoid recipients are likely to be receiving multiple chemical agents, experiencing direct and/or indirect neuropsychiatric complications from the disease process itself, possess a changing interpersonal milieu, and may be having marked psychological reactions to the disease's prognosis [15]. The mechanism by which the glucocorticoids induce behavioral disturbances is still largely unknown [25].

Glucocorticoid-induced behavioral sequelae were thus judged as worthy of further analysis. The performance of laboratory rats in several simple tests was selected as an assay with which to assess the effects of prednisolone, a commonly used synthetic glucocorticoid. It was reasoned that if such behavioral sequelae could be routinely produced in a laboratory model then identification of mechanisms of behavioral action, selective antagonists, and adverse behavioral drug interactions might be expedited. Specifically, the present study examined the effects of the varying of dose of repeated, daily prednisolone treatments upon water intake, body and organ weights, and measures of locomotion, nocioception, and grasping response.

METHOD

Subjects

Twenty-four male Sprague-Dawley rats of 33–35 days of age, and bred and raised in this laboratory's colony, served as subjects. Rapidly growing rats were selected in an

effort to maximize potential evidence of systemic toxicity. Subjects were individually housed under constant temperature (ca. 23° C) and illumination. Purina Laboratory Chow (Rat Chow 5012, Ralston Purina Co., St. Louis, MO) and water were continuously available for all subjects.

Apparatus

Water intake monitors. Water intake was measured via modified 50-ml disposable syringes functioning as fluid reservoirs (Becton-Dickinson, Rutherford, NJ; model #Bect-5605). The syringe barrels, with plungers removed, were plugged with no. 5 rubber stoppers and associated drink spouts, and were then occluded at the needle end by heating. These reservoirs were subsequently filled with water, inverted, and attached to individual, stainless steel cages (32×24×20 cm; Unifab Corp, Kalamazoo, MI).

Total body weights. Individual body weights were determined daily with a top-loading scale (Pelouze, Model 1000).

Locomotion. Motor activity was measured for each subject's performance on one of three standard Wahmann Running Wheels (Wahmann Co., Baltimore, MD). Each wheel (35 cm dia. × 11 cm wide) was equipped with a microswitch which electronically sensed revolutions of both directions. Running wheels were placed in separate, sound-attenuating chambers (61×61×61 cm) equipped with masking white noise (80 dB), forced-air ventilation, and illumination (7.5 watt G. E.).

Nocioception. An electrically heated metal floor (63×16×9.5 cm; model #26000, Chicago Surgical and Electrical Co., Chicago, IL) surrounded by three wooden walls (21.5×63×2.0 cm) and a fourth transparent acrylic wall (21.5×63×0.6 cm) served. The floor was heated to ca. 59° C. Latencies to hind paw-lick were assessed by an observer who terminated a running time meter upon each occurrence of the behavior.

Grasping response. Subjects were suspended by forepaw-grasp from a 0.013-cm dia. wire, 43 cm above a floor. Latencies from the moment of grasping to the release of the grasp were assessed by an observer who operated a running time meter.

Adrenal and gonad weights. Excised glands were weighed on a Mettler H54 Analytical Balance (Mettler Co., Switzerland).

Procedure

Water intake and body weight measurements. Water intake was monitored by noting net changes in milliliters absent from fluid reservoirs over 20 consecutive 24-hour periods. At the end of each 24-hour period, reservoirs were emptied and then re-filled with fresh water. An initial 8-day acclimation period to this procedure occurred. Subsequently, twelve daily body weight assessments and intramuscular injections were performed for each subject at the time of intake measurement.

Locomotion, grasping response, and nocioception. After twelve days of injections, a series of behavioral tests were performed with each rat. Subjects were injected and 30 minutes later placed in running wheels for an additional 30 minutes. Immediately after this, the grasping response tests were conducted. In this assay each subject was moved manually in a downward vertical direction; the wire to be grasped was positioned immediately in front of the subject. When the subject grasped the wire, the animal was released and thus was suspended by the forepaws. Latencies, from this moment until the subject dropped from the wire, were recorded. One-minute intervals occurred between trials. Five such trials, conducted in succession for each subject, occurred. Trials were restricted to 3.0 minutes at maximum.

Following completion of the grasping-response assessment, each subject was studied in the hot-plate analgesia test. Latencies to hind paw-lick were analyzed by exposing each subject to five trials, each of a maximum 30-second duration, and separated by inter-trial intervals of 2.0 minutes. As a subject was placed on the hot-plate, a running time meter was concurrently activated; when the subject licked either of its hind paws the meter was switched off.

Organ Weights

Following completion of behavioral tests on day 12 of study, subjects were sacrificed under deep ether anesthesia; adrenal and gonadal glands were then excised and weighed in pairs for each animal. The weights of the organ pairs were reported as single units and as units relative to the body weights on day 12.

Drug Preparation and Administration

Stock suspensions of prednisolone acetate (50 mg/ml) (Carter-Glogan, Glendale, AZ) were diluted with physiological saline to concentrations of 8.0, 16.0, and 32.0 mg/ml and administered at 1.0 ml/kg volumes by intramuscular injections. Dosage levels of 0.0, 8.0, 16.0, and 32.0 mg/kg were employed with four groups of subjects (N=6/group) each receiving one. This dose range was selected by reference to previous prednisolone studies which used rat subjects (e.g., [31,43]). All injections occurred at the beginning of the 24-hour water intake periods, and 30 minutes before exposure to the wheel-running apparatus on the day of acute behavioral tests (drug day 12).

Statistical Analysis

Daily water intake and body weight data, and the results of the grasping response and nocioception assays, were analyzed by use of repeated measures analysis of variance [17]. Prednisolone effects upon adrenal, gonadal, and body weights (day 12), relative glandular weights, and locomotion were assessed by one-way analysis of variance (ANOVA) techniques. Analysis of variance tests were followed by Tukey Simultaneous Testing procedures and Least Significant Difference tests [17]. Assay results were reported graphically as group means±standard errors (N=6/group).

RESULTS

Prednisolone Effects on Water Intake

Daily administrations of prednisolone acetate at all dosage levels examined produced a general decrease in water intake, as compared to control intake. As shown in Fig. 1, water intake for saline-treated subjects demonstrated relative stability, while the intake for drug-treated groups showed a progressive decay. Two-way repeated measures ANOVA indicated that there were significant effects regarding dosage level, $F(3,23)=6.731$, $p<0.003$, number of treatments, $F(9,216)=8.914$, $p<0.001$, and of a dose-by-treatments interaction, $F(27,216)=3.745$, $p<0.001$. For higher dose groups (16.0 and 32.0 mg/kg) a partial recovery of water intake occurred during latter sessions.

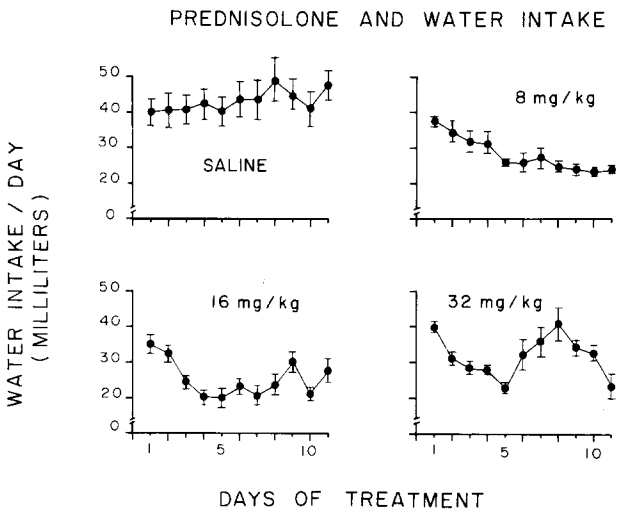

FIG. 1. Effects of daily prednisolone treatments upon number of milliliters of water intake per day. "Day 1" entitles the mean number of milliliters consumed over the last 3 days of the baseline period. For all subsequent data points, drug injections occurred immediately before each 24-hr observation period. Each point represents a group mean±standard error (N=6/group).

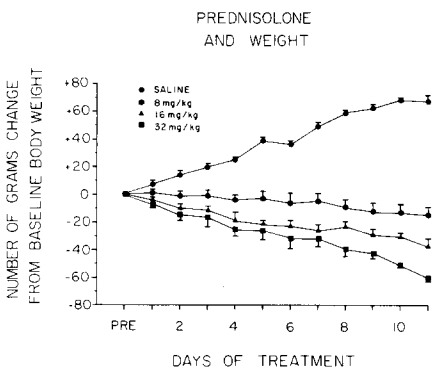

FIG. 2. Effects of daily prednisolone administrations upon average changes in body mass across treatment groups. "Pre" entitles that baseline from which all weight changes are calculated. Each subsequent weight determination follows by 24 hours the preceding injection. Each data point (Days 1–11) is a group mean ±standard error (N=6/group).

Prednisolone Effects on Body Weight

In addition, daily prednisolone treatments produced clear indications of accruing, dose-related, systemic toxicities as evidenced by progressive loss in total body mass. These effects are displayed in Fig. 2 where mean number of grams change (Mean±S.E.) from baseline body weights is plotted as a function of number of days of drug treatment for each dose group. Thus, whereas the saline-treated subjects gained 66.7±5.5 g throughout the study period, the 8.0 mg/kg group lost 14.7±5.6 g; the 16.0 mg/kg group lost 35.7±3.6 g; and the 32.0 mg/kg group lost 56.3±5.2 g. A two-way repeated measures ANOVA indicated a highly significant main effect of dosage level, $F(3,23)=78.377$, $p<0.001$, a significant effect

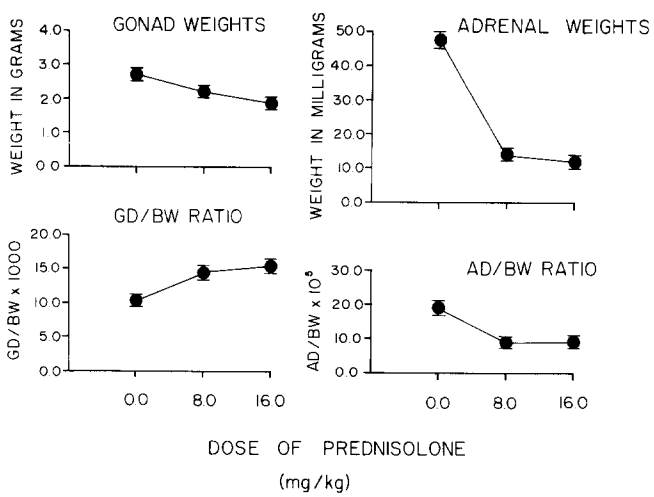

FIG. 3. Effects of dose of twelve daily prednisolone treatments upon both absolute and relative adrenal and gonadal weights. Each data point is a group mean±standard error (N=6/group).

of number of treatments, $F(11,264)=5.691$, $p<0.001$, and a significant dose by treatments interaction, $F(33,220)=52.419$, $p<0.001$. The dose-effect function relating dosage of prednisolone to day 12 body weight is displayed graphically in Fig. 4 with an N of 6 per group. A one-way ANOVA indicated these differences to be significant, $F(3,20)=125.515$, $p<0.001$.

Prednisolone Effects on Organ Weights

Figure 3 presents the effects of dose of drug treatment upon the absolute and relative weights for excised pairs of adrenals and gonads. The 32.0 mg/kg group was judged as too debilitated at drug day 12 for further analysis; thus organ weights and Day 12 behavioral tests were omitted for those subjects. A one-way ANOVA procedure assessing average absolute weights of paired adrenal glands indicated these results to be significantly different across groups, $F(2,15)=119.625$, $p<0.001$. The Tukey Simultaneous Testing procedure demonstrated that it was the saline-treated subjects which differed significantly ($p<0.001$). The adrenal-to-body weight (mg/kg) ratios also demonstrated clear effects of drug dosage level. The one-way ANOVA procedure showed these results to differ significantly $F(2,15)=41.662$, $p<0.001$. As displayed in Fig. 3, these results indicated that as dose increased the adrenal glands atrophied at a higher rate than that which was experienced by the body overall.

As shown in Fig. 3, gonads, like adrenals, decreased further in absolute weight as the dose of prednisolone increased. One-way ANOVA procedures indicated these effects to be significantly different $F(2,15)=17.163$, $p<0.001$. The Tukey Simultaneous Testing procedure further showed saline-treated subjects' testes to weigh more than the 8.0 mg/kg gonads ($p<0.05$) and those of the 16.0 mg/kg treatment group ($p<0.01$), with the 8.0 mg/kg glands weighing significantly more than those of the 16.0 mg/kg group ($p<0.05$). Inspection of relative gonadal weights (testes (g) to total body weight (g)) indicated that as dosages increased the relative gonadal weights also increased. The average relative gonadal

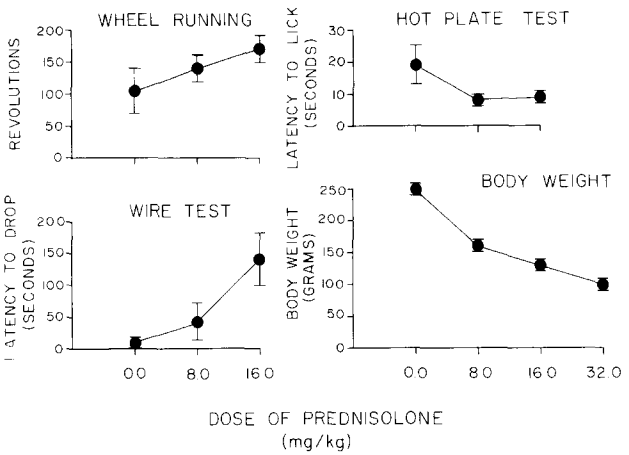

FIG. 4. Effects of dose of twelve daily prednisolone treatments upon four serial assays: 30-minute wheel running; grasp-release measure; hot-plate analgesia assay; and body weights on Day 12. Each data point represents a group mean±standard error (N=6/group).

weight ratios across the 0.0, 8.0, and 16.0 mg/kg groups were significantly different: one-way ANOVA, $F(2,15)=21.149$, $p<0.001$, with the saline group differing from both the 8.0 and 16.0 mg/kg subjects (Tukey: $p<0.01$ in both cases). The most influential determinant of the direct nature of the relationship between dose and gonad-to-body weight ratios is to be noted by inspection of Figs. 2 and 3. The two collectively reveal that total body mass decayed more quickly than gonads, per se. These results with gonads contrast with the opposite results involving adrenal-to-body weight ratios. By comparing relative adrenal to relative gonad weights across dosage groups, it is evident that the adrenals sustained specific degeneration when compared to both another endocrine gland and general body mass.

Prednisolone Effects on Locomotion, Grasping Response, and Nocioception

Assays of locomotor activity, grasping responses, and analgesia were conducted on the twelfth day of study for all subjects, except the 32.0 mg/kg group as previously noted. The results of these three assays are presented in Fig. 4. Locomotor performances in 30-minute running wheel sessions were assessed using one-way ANOVA procedures and these results were found to approach, but not reach, statistical significance, $F(2,15)=2.338$, $p<0.131$. Marked variability within groups bore a direct relation to this lack of significance. Visual observation of subjects in the home cages revealed, however, a seemingly dose-related increase in ambulation and "darting," and an overall "frenetic" appearance.

Evaluation of the grasping response revealed significant dose-related increases in the latency to release grasp of the wire: two-way repeated measures ANOVA, effect of drug dose, $F(2,17)=5.583$, $p<0.015$. However, there was no effect as a function of number of trials, $F(3,72)=0.861$, $p<0.161$, or of a dose-by-trials interaction, $F(8,60)=1.546$, $p<0.161$. The effects of dosage level upon latency to drop are presented graphically for the 0.0, 8.0, and 16.0 mg/kg groups (N=6/group) in Fig. 4.

Results of the assessment of nocioception by use of the hot-plate method are presented in Fig. 4. Two-way repeated measures ANOVA showed that the main effect of dosage level approached but did not reach statistical significance, $F(2,17)=2.569$, $p<0.110$. No effects of either the number of trials, $F(4,72)=0.376$, $p<0.825$, or of an interaction between dosage and trial number, $F(8,60)=0.753$, $p<0.645$, were observed.

DISCUSSION

Daily prednisolone yielded decrements in water intake which accrued both as a function of drug dose and number of treatments. Also observed was a significant interaction between these two variables (Fig. 1). One potential mechanism may reside with known glucocorticoid effects on electrolyte balance [18]. Glucocorticoid treatment yields sodium reabsorption in the kidney's distal tubules [18]. High levels of glucocorticoids also reduce sodium concentration and sodium/potassium ratios in *in vivo* dialysate of stool [41]. Therefore, marked sodium retention occurs by both renal and gastrointestinal processes. As sodium is retained, water passively follows and extracellular fluid volumes rise [18]. Antidiuretic hormone (ADH) synthesis and release mechanisms may also be activated yielding further renal reabsorption of water [16]. Thus, cortisol typically enhances total body water, most often in the extracellular space, but also on occasion in intracellular compartments [53]. In contrast to cortisol and corticosterone, prednisolone and prednisone yield comparatively weak sodium retention, yet clinically evident edema does occur and particularly with high doses (e.g., [30]). Prednisolone-induced increases in extracellular volumes may thus yield prolonged suppression of drinking by altering volumetric thirst mechanisms. These mechanisms have been analyzed [10, 11, 47, 48].

Both the 16.0 and 32.0 mg/kg subjects demonstrated a partial return toward baseline intake during latter days (Fig. 1). The significance and causal mechanism of such effects remain unclear. It is possible that volume receptor activity became adapted and thus yielded a decline in both ADH release and the typical renal sequela to ADH release [16]. Alternately, extended glucocorticoid treatment can yield both shifts in the internal distribution of water by altering membrane's permeability to water [30] and increased renal free water clearance [7]. Additionally, intake modulation may occur via direct action of glucocorticoids on the CNS, perhaps at the level of the hypothalamus, as extensive binding of glucocorticoids upon CNS tissues has been demonstrated [9,28].

Daily prednisolone treatment produced dose-related systemic toxicities, as indexed by marked decrements in total body mass. Weight loss accrued with number of drug treatments, and a dose-by-treatments interaction was demonstrated (Fig. 2). Although Cushingoid patients typically present mild-to-dramatic weight gains, various reports have indicated weight loss subsequent to glucocorticoid treatment in laboratory animals [19, 20, 23, 27, 33]. In this catabolic effect, glucocorticoid actions appear to be multiple, or at least to affect multiple systems.

Well-known are glucocorticoid effects upon protein metabolism (e.g., [1,27]). Decrements in protein stores occur for almost all tissues except liver [16], along with increased mobilization of amino acids from extrahepatic tissues [18,36], skeletal muscle wasting [18,44], and a negative ni-

trogen balance [44] due in part to amino acid deamination [1,36]. Also, high circulating glucocorticoid levels produce inhibition of protein synthesis [1,6], possibly related to observed decrements in extrahepatic RNA formation [16] and/or amino acid uptake [1, 6, 22]. In the present experiment, postmortem inspections revealed marked wasting of skeletal muscle in drug-treated subjects. Altered protein metabolism is thus suggested as one important mediator of the prednisolone-induced weight losses here reported.

A second plausible mechanism of the present weight losses may involve a drug-induced abatement of growth. Widespread inhibition of growth has been reported for both child [3, 8, 24, 50] and immature laboratory animal [52] recipients of glucocorticoid therapy. In these, prolonged high-dose glucocorticoids have produced decreased height, body mass, and skeletal maturity [3]. Glucocorticoid treatment may result in premature closure of the epiphysial plates of long bones, thus yielding an irreversible shortening of stature [24]. In addition, osteoporosis occurs [24,50], probably as a consequence of catabolism and anti-anabolism of bone's protein matrix [16]. Inhibition of growth hormone secretion follows glucocorticoid treatment, yet because replacement therapy does not restore growth, little relevance has been assigned this sequela [1,32]. Subsequent to glucocorticoid administration, decreased cell division and DNA synthesis have been documented across various tissues [18], with effects particularly evident where cell proliferation represents accremental, as opposed to turn-over, growth [27]. Exactly how these effects are mediated remains obscure [18]. The present study employed 30-day old weanling rats; organisms in which very rapid growth occurs (with a doubling of body mass in about 2 weeks) [27]. Thus, the marked differences in weight across groups noted in the present study might have been in part a function of the arresting of growth in the prednisolone-treated subjects.

Still other hypothesized mediators of prednisolone's body weight effects involve modification of intake and excrement processes. Already discussed has been this drug's effect on water intake as shown in our assay. Clear dose-related decrements in water-intake were noted, and it is plausible that this adipsia contributed to overall losses in body mass. Another line of evidence suggests that glucocorticoid-induced alterations in food intake also contributed. Severe calorie deprivation induces increased levels of circulating glucocorticoids with resultant decreased rate of somatic growth noted in immature laboratory animals and children [40]. Second, adrenalectomy decreases food intake, and glucocorticoid replacement therapy restores intake to control levels [23]. Third, patients receiving glucocorticoid therapy for palliation of various chronic disease states demonstrate marked enhancements of "appetite" following therapy onset [1]. The interpretation of this latter evidence is clouded however, as alleviation of the disease state per se might alter intake patterns. Direct analysis of exogenous corticosterone effects upon feeding by laboratory animals has revealed a bitonic function. Low doses of corticosterone stimulate, whereas high doses suppress, food intake [35,51]. Panksepp [35] has speculated that low doses induce hyperglycemia which in turn yields insulin secretion and increased feeding, whereas high doses induce profound hyperglycemia and a resultant cessation of feeding. As prednisolone is at least 3–4 times more potent than the naturally occurring glucocorticoids with respect to carbohydrate metabolism effects [18], it is likely that the dose range employed in the present study rests more on the aphagic extreme of this bitonic function. Direct observations of food intake under prednisolone treatment are required for further analysis.

Prednisolone displayed selective effects in both across-organ and relative organ weight comparisons (Fig. 3). Absolute gonadal weights were depressed in a dose-related fashion for drug-treated versus control subjects. Yet when gonad-to-total body weight ratios were examined, the testes were found to be relatively insensitive to glucocorticoid effects. This latter result is in keeping with reports describing the testes as "glucocorticoid-resistant" [27]. Drug-treated subjects were also found to possess decreased absolute and relative adrenal weights as compared to saline control subjects. Thus, although prednisolone depressed body weights, adrenal mass was depressed at a faster rate. Similar results have been obtained with other glucocorticoids [19, 20, 23, 42]. It is well-known that continued high doses of exogenous glucocorticoids generally suppress ACTH secretion via feedback inhibition mechanism(s) [13]. Subsequent to ACTH suppression, the adrenal cortex undergoes atrophy, largely in the region of the zona fasiculata [18].

At what level(s) of the hypothalamo-pituitary axis the glucocorticoids exert their ACTH suppressive effect remains to be elucidated [1]. Glucocorticoid binding has been demonstrated in pituitary, hypothalamus, and other brain regions [29]. Some evidence exists to suggest that the glucocorticoids feed back to suppress secretion of the so-called "31-K precursor" pro-hormone [21]. Systemically administered dexamethasone has been shown to decrease beta-endorphin (component of precursor) content of the pituitary [14]. Further, depletion of pituitary stores of endorphin via other procedures has been shown to yield hyperalgesia. For instance, hypophysectomy decreases the intensity of inescapable shock to which rats will respond [12]. Thus, the tendency toward hyperalgesia noted in the hot-plate assay (Fig. 4) may have been due to prednisolone's feedback inhibition of the 31-K precursor. This plausibility awaits analysis.

The data relating prednisolone to wheel-running activity revealed a direct, linear function which approached, but did not reach, statistical significance (Fig. 4). That some relation between prednisolone administration and locomotion exists might have been anticipated as various clinical reports of "steroid psychosis" have detailed psychomotor agitation in glucocorticoid-treated patients [5, 15, 18]. In addition, studies of wheel running in rats receiving either replacement doses of corticosterone [23] or pharmacological doses of dexamethasone [2,20] have demonstrated activity enhancement. In those two studies where dexamethasone was given [2,20], wheel running was enhanced to a degree greater than that reported in the present study for prednisolone. At least two possible accounts of this difference may be offered. First, these two glucocorticoids may possess differing potencies with respect to locomotor stimulation. Alternately, a procedural variable might be a crucial determinant of across-reports differences. In both [2,20] previous studies, many wheel-running sessions were conducted before and during glucocorticoid administration. In the present study, only a single session was conducted. It may be that drug treatment interacts with previous history in the test apparatus to determine test outcome.

As noted, the glucocorticoids yield overall protein-wasting, resulting from both proteolysis and inhibition of protein synthesis. As a consequence, mild-to-dramatic wasting of skeletal muscle is common in cases of both endogenous and iatrogenic Cushing's syndrome [34,38]. As men-

tioned, our gross postmortem carcass inspections revealed considerable absence of skeletal muscle in drug-treated subjects. In clinical cases such wasting is particularly marked in proximal regions of arms and legs and may occur shortly after treatment initiation and be severe enough to prevent ambulation [18]. Thus, we had expected that prednisolone-treated subjects would have a much shorter latency to grasp-release upon elevated suspension than control subjects so treated. This result was not obtained, but rather, as prednisolone dose increased, so too did latency to grasp-release (Fig. 4).

The determinants of this obtained relation are not immediately obvious, though two possibilities suggest themselves. One is that the results of our "wire test" assay of grasping are the trivial consequences of decreased body mass. Note that those groups with longest latency to grasp-release were also those that weighed least and thus had the least mass to support (note Fig. 4, Body Weight, Day 12). Alternately, various other investigations have shown exogenous glucocorticoid treatment to alter passive avoidance. It might be that prednisolone-treated subjects retained grasp longer as a result of an enhancement of those processes involved in passive avoidance. Glucocorticoids have generally been shown however, to decrease passive avoidance performances [4]. Further analysis of this effect upon grasping responses will require appropriate weight control groups.

In summary, the present study demonstrated prednisolone as active in several behavioral assays employing rodents. It is plausible that such assays might be useful in subsequent studies attempting identification of selective antagonists of, and other drugs interactive with, this agent.

ACKNOWLEDGEMENTS

The authors wish to thank members of the Laboratory in the Behavioral Effects of Cancer Therapy for their helpful comments during preparation of the manuscript, and Vivian Farah for her editorial assistance. Science Graphics (Kalamazoo, MI) is here acknowledged for provision of the figures.

REFERENCES

1. Baxter, J. D. and P. H. Forsham. Tissue effects of glucocorticoids. *Am. J. Med.* **53:** 573–589, 1972.
2. Beatty, W. W., C. W. Scouten and P. A. Beatty. Differential effects of dexamethasone and body weight loss on two measures of activity. *Physiol. Behav.* **7:** 869–871, 1971.
3. Blodgett, F. M., L. Burgin, D. Iezzoni, D. Gribetz and N. B. Talbot. Effects of prolonged cortisone therapy on the structural growth, structural maturation and metabolic status of children. *New Engl. J. Med.* **254:** 636–641, 1956.
4. Bohus, B. Pituitary-adrenal influences on avoidance and approach behavior of the rat. In: *Progress in Brain Research*, vol. 39, *Drug Effects on Neuroendocrine Regulation*, edited by E. Zimmerman, W. H. Gispen, B. H. Marks, and D. DeWied. New York: Elsevier, 1973, pp. 406–420.
5. Brown, J. Effects of steroids on metabolism of carbohydrate, protein, and fat. In: *Clinical Uses of Adrenal Steroids*, edited by J. Brown and C. M. Pearson. New York: McGraw-Hill, 1962, pp. 399–431.
6. Clark, I. The effects of cortisone upon protein synthesis. *J. biol. Chem.* **200:** 69–76, 1953.
7. Dingham, J. F. Adrenal steroids and water metabolism. In: *Inflammation and Diseases of Connective Tissue*, edited by L. C. Mills and J. H. Moyer. Philadelphia: Saunders, 1961, pp. 390–396.
8. Falliers, C. J., L. S. Tan, J. Szentivanyi, J. R. Jorgensen and S. C. Bukantz. Childhood asthma and steroid therapy as influences on growth. *Am. J. Dis. Child.* **105:** 127–137, 1963.
9. Feldman, S. The integration of neural and endocrine factors regulating hypothalamic activity. In: *Brain-Pituitary-Adrenal Interrelationships*, edited by A. Brodish and E. S. Redgate. New York: S. Karger, 1973, pp. 224–238.
10. Fitzsimons, J. T. Drinking by rats depleted of body fluid without increase in osmotic pressure. *J. Physiol*, Lond. **159:** 297–309, 1961.
11. Gilbert, G. J. and G. H. Glaser. On the nervous system integration of water and salt metabolism. *Archs. Neurol.* **5:** 179–196, 1961.
12. Gispen, W. H., Tj. B. Van Wimersma Greidanus and D. DeWied. Effects of hypophysectomy and $ACTH_{1-10}$ on responsiveness to electric shock in rats. *Physiol. Behav.* **5:** 143–146, 1970.
13. Graber, A. L., R. E. Ney, W. E. Nicholson, D. P. Island and G. W. Liddle. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. *J. clin. Endocr. Metab.* **25:** 11–16, 1965.
14. Guillemin, R., T. Vargo, J. Rossier, S. Minick, N. Ling, C. Rivier, W. Vale and F. Bloom. Beta-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* **197:** 1367–1369, 1977.
15. Guynn, R. W. Steroidal drugs. In: *Neuropsychiatric Side-Effects of Drugs in the Elderly (Aging*, vol. 9), edited by A. J. Levenson. New York: Raven Press, 1979, pp. 123–150.
16. Guyton, A. C. *Medical Physiology*, 5th ed. Philadelphia: Saunders, 1979.
17. Hayes, W. L. *Statistics*, New York: Holt, Rinehart, and Winston, 1963.
18. Haynes, R. C., Jr. and F. Murad. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogues; inhibitors of adrenocortical steroid biosynthesis. In: *The Pharmacological Basis of Therapeutics*, 6th ed., edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: MacMillan, 1980, pp. 1466–1496.
19. Katz, R. J. and B. J. Carroll. Endocrine control of psychomotor activity in the rat: Effects of chronic dexamethasone upon general activity. *Physiol. Behav.* **20:** 25–30, 1978.
20. Kendall, J. W. Dexamethasone stimulation of running activity in the male rat. *Hormones Behav.* **1:** 327–336, 1970.
21. Krieger, D. T., A. S. Liotta, M. J. Brownstein and E. A. Zimmerman. ACTH, beta-lipotropin, and related peptides in brain, pituitary and blood. In: *Recent Prog. Horm. Res.* **36:** 277–344, 1980.
22. Lawrence, A. W. and R. MacVicar. Effect of cortisone upon protein synthesis in the rat. *Fedn. Proc.* **13:** 248–249, 1954.
23. Leshner, A. I. The adrenals and the regulatory nature of running wheel activity. *Physiol. Behav.* **6:** 551–558, 1971.
24. Liddle, G. W. and K. L. Melman. The adrenals. In: *Textbook of Endocrinology*, 5th ed., edited by R. H. Williams. Philadelphia: Saunders, 1974, pp. 233–282.
25. Ling, M. H. M., P. J. Perry and M. T. Tsuang. Side effects of corticosteroid therapy. *Archs. gen. Psychiat.* **38:** 471–477, 1981.
26. Livingston, R. B. and S. K. Carter. *Single Agents in Cancer Chemotherapy*. New York: Plenum, 1970, pp. 337–358.
27. Loeb, J. N. Corticosteroids and growth. *New Engl. J. Med.* **295:** 547–552, 1976.
28. McEwen, B. S. Glucocorticoid binding sites in rat brain: Subcellular and anatomical localizations. In: *Progress in Brain Research*, vol. 39, *Drug Effects on Neuroendocrine Regulation*, edited by E. Zimmerman, W. H. Gispen, B. H. Marks and D. DeWied. New York: Elsevier, 1973, pp. 87–97.
29. McEwen, B. S. Adrenal steroid feedback on neuroendocrine tissues. *Ann. N.Y. Acad. Sci.* **297:** 568–579, 1977.
30. Mills, L. C. Adrenal cortex and adrenocortical hormones. In: *Drill's Pharmacology in Medicine*, 3rd ed., edited by J. R. Dipalma. New York: McGraw-Hill, 1965, pp. 1182–1230.
31. Moore, P. K. and J. R. S. Hoult. Anti-inflammatory steroids reduce tissue PG synthetase activity and enhance PG breakdown. *Nature* **288:** 269–270, 1980.

32. Morris, H. G., J. R. Jorgensen, H. Elrick and R. E. Goldsmith. Metabolic effects of human growth hormone in corticosteroid-treated children. *J. clin. Invest.* **47:** 436–451, 1968.
33. Nelson, D. H. Cushing's syndrome. In: *Endocrinology,* vol. 2, edited by L. J. DeGroot, G. F. Cahill, Jr., W. D. Odell, L. Martini, J. T. Potts, Jr., D. H. Nelson, E. Steinberger and A. I. Winegrad. New York: Grune and Stratton, 1979, pp. 1179–1192.
34. Nelson, D. H. *The Adrenal Cortex: Physiological Function and Disease.* Philadelphia: Saunders, 1980, pp. 134–176.
35. Panksepp, J. Hormonal control of feeding behavior and energy balance. In: *Hormonal Correlates of Behavior,* vol. 2, edited by B. E. Eleftheriou and R. L. Sprott. New York: Plenum Press, 1975, pp. 657–695.
36. Parson, W., K. R. Crispell and A. Ebbert, Jr. Abnormalities in N 15 excretion rates after ingestion of tagged glycine in Cushing's syndrome and following ACTH administration. *J. clin. Invest.* **31:** 548–554, 1952.
37. Pearson, C. M. Muscle and hormones. In: *Textbook of Endocrinology,* 5th ed., edited by R. H. Williams. Philadelphia: Saunders, 1974, pp. 994–1003.
38. Perkoff, G. T., R. Silber, F. H. Tyler, G. E. Cartwright and M. M. Wintrobe. Studies in disorders of muscle: XII. Myopathy due to administration of therapeutic amounts of 17-hydroxycorticosteroids. *Am. J. Med.* **26:** 891–898. 1959.
39. Peterson, L. G. and M. K. Popkin. Neuropsychiatric effects of chemotherapeutic agents in cancer. *Psychosomatics* **21:** 141–153, 1980.
40. Prader, A., J. M. Tanner, G. A. von Harnack. Catch-up growth following illness or starvation: An example of developmental canalization in man. *J. Pediat.* **62:** 646–659, 1963.
41. Richards, P. Clinical investigation of the effects of adrenal corticosteroid excess on the colon. *Lancet* **1:** 437–443, 1969.
42. Salassa, R. M., W. A. Bennet, F. R. Keating, Jr. and R. G. Sprague. Postoperative adrenal cortical insufficiency; occurrence in patients previously treated with cortisone. *J. Am. Med. Assoc.* **152:** 1509–1515, 1953.
43. Sanders, D. B., T. R. Johns, M. E. Eldefrawi and E. E. Cobb. Experimental autoimmune myasthenia gravis in rats. *Archs. Neurol.* **34:** 75–79, 1977.
44. Siber, R. H. and C. C. Porter. Nitrogen balance, liver protein repletion, and body composition of cortisone-treated rats. *Endocrinology* **52:** 518–526, 1953.
45. Smith, C. K., J. Barish, J. Correa and R. H. Williams. Psychiatric disturbance in endocrinologic disease. *Psychosom. Med.* **34:** 69–86, 1972.
46. Stewart, D. J. and R. S. Benjamin. Cancer chemotherapeutic agents. In: *Neuropsychiatric Side-Effects of Drugs in the Elderly, (Aging,* vol. 9) edited by A. J. Levenson. New York: Raven Press, 1979, pp. 191–224.
47. Stricker, E. M. Extracellular fluid volume and thirst. *Am. J. Physiol.* **211:** 232–238, 1966.
48. Stricker, E. M. Osmoregulation in rats: inhibition of hypovolemic thirst by water. *Am. J. Physiol.* **217:** 98–105, 1969.
49. Tepperman, J. *Metabolic and Endocrine Physiology,* 4th ed. Chicago: Yearbook Medical Pub., 1980, pp. 167–221.
50. Thomas, J. A. and M. G. Mawhinney. *Synopsis of Endocrine Pharmacology.* Baltimore: University Park Press. 1973, pp. 161–182.
51. Van Putten, L. M., D. W. Van Bekkum and A. Querido. Influence of cortisone and ACTH on appetite. *Acta endocr.* **12:** 159–166, 1953.
52. Wells, B. B. and E. C. Kendall. The influence of corticosterone and C_{17} hydroxydehydrocorticosterone (compound E) on somatic growth. *Proc. Staff Meet. Mayo Clin.* **15:** 324–328, 1940.
53. Ziff, M., J. Simson and J. J. Bunim. Effect of ACTH on water distribution in man as measured by antipurene T-1824, and bromide. *J. clin. Invest.* **31:** 829–839, 1952.