[Template:Distinguish2](/wiki/Template:Distinguish2" \o "Template:Distinguish2) [Template:Drugbox](/wiki/Template:Drugbox)

**Cortisol** is a [steroid hormone](/wiki/Steroid_hormone), in the [glucocorticoid](/wiki/Glucocorticoid) class of hormones, and is produced in humans by the [zona fasciculata](/wiki/Zona_fasciculata) of the [adrenal cortex](/wiki/Adrenal_cortex) within the [adrenal gland](/wiki/Adrenal_gland).<ref name=About>[Template:Cite web](/wiki/Template:Cite_web)[Template:Better source](/wiki/Template:Better_source)</ref> It is released in response to [stress](/wiki/Stress_(biology)) and low [blood-glucose concentration](/wiki/Blood_sugar).

It functions to increase [blood sugar](/wiki/Blood_sugar) through [gluconeogenesis](/wiki/Gluconeogenesis), to suppress the [immune system](/wiki/Immune_system), and to aid in the [metabolism](/wiki/Metabolism) of [fat](/wiki/Fat), [protein](/wiki/Protein), and [carbohydrates](/wiki/Carbohydrates).[[1]](#cite_note-1) It also decreases bone formation.[[2]](#cite_note-2) **Hydrocortisone** ([INN](/wiki/International_Nonproprietary_Name), [USAN](/wiki/United_States_Adopted_Name), [BAN](/wiki/British_Approved_Name)) is a name for cortisol when it is used as a medication. Hydrocortisone is used to treat people who lack adequate naturally generated cortisol. It is on the [World Health Organization's List of Essential Medicines](/wiki/World_Health_Organization's_List_of_Essential_Medicines), the most important medications needed in a basic [health system](/wiki/Health_system).[[3]](#cite_note-3)

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## Health effects[[edit](/index.php?title=(none)&action=edit&section=1)]

### Metabolic response[[edit](/index.php?title=(none)&action=edit&section=2)]

In the early [fasting](/wiki/Fasting) state, cortisol stimulates [gluconeogenesis](/wiki/Gluconeogenesis) (the formation of glucose), and activates anti-stress and anti-inflammatory pathways.[[4]](#cite_note-4) Cortisol also plays an important, but indirect, role in liver and muscle [glycogenolysis](/wiki/Glycogenolysis), the breaking down of [glycogen](/wiki/Glycogen) to [glucose-1-phosphate](/wiki/Glucose-1-phosphate) and glucose. This is done through its passive influence on [glucagon](/wiki/Glucagon).[Template:Clarify](/wiki/Template:Clarify) Additionally, cortisol facilitates the activation of [glycogen phosphorylase](/wiki/Glycogen_phosphorylase), which is necessary for epinephrine to have an effect on glycogenolysis.[[5]](#cite_note-5)[[6]](#cite_note-6) In the late fasting state, the function of cortisol changes slightly and *increases* [glycogenesis](/wiki/Glycogenesis). This response allows the liver to take up glucose that is not being used by the peripheral tissue and turn it into liver glycogen stores to be used if the body moves into the starvation state.[Template:Citation needed](/wiki/Template:Citation_needed)

Elevated levels of cortisol, if prolonged, can lead to [proteolysis](/wiki/Proteolysis) (breakdown of proteins) and muscle wasting.[[7]](#cite_note-7) Several studies have shown that cortisol can have a [lipolytic](/wiki/Lipolysis) effect (promote the breakdown of fat). Under some conditions, however, cortisol may somewhat suppress lipolysis.[[8]](#cite_note-8)

### Immune response[[edit](/index.php?title=(none)&action=edit&section=3)]

Cortisol prevents the release of substances in the body that cause inflammation. It is used to treat conditions resulting from over activity of the B-cell-mediated antibody response. Examples include inflammatory and [rheumatoid](/wiki/Rheumatoid) diseases, as well as [allergies](/wiki/Allergy). Low-potency hydrocortisone, available as a non-prescription medicine in some countries, is used to treat skin problems such as [rashes](/wiki/Rashes), and [eczema](/wiki/Eczema).

It inhibits production of [interleukin (IL)-12](/wiki/Interleukin_12), [interferon (IFN)-gamma](/wiki/Interferon_gamma), IFN-alpha and [tumor-necrosis-factor (TNF)-alpha](/wiki/Tumor_necrosis_factor_alpha) by antigen-presenting cells (APCs) and [T helper (Th)1 cells](/wiki/T_helper_cell), but upregulates [IL-4](/wiki/Interleukin_4), [IL-10](/wiki/Interleukin_10), and [IL-13](/wiki/Interleukin_13) by Th2 cells. This results in a shift toward a Th2 immune response rather than general immunosuppression. The activation of the stress system (and resulting increase in cortisol and Th2 shift) seen during an infection is believed to be a protective mechanism which prevents an over activation of the inflammatory response.[[9]](#cite_note-9) Cortisol can weaken the activity of the [immune system](/wiki/Immune_system). Cortisol prevents proliferation of T-cells by rendering the [interleukin-2](/wiki/Interleukin-2) producer [T-cells](/wiki/T-cell) unresponsive to [interleukin-1](/wiki/Interleukin-1) (IL-1), and unable to produce the T-cell growth factor ([IL-2](/wiki/Interleukin_2)).[[10]](#cite_note-10) Cortisol also has a negative-feedback effect on interleukin-1.[[11]](#cite_note-11) Though IL-1 is useful in combating some diseases; however, [endotoxic](/wiki/Endotoxin) bacteria have gained an advantage by forcing the [hypothalamus](/wiki/Hypothalamus) to increase cortisol levels (forcing the secretion of [CRH](/wiki/Corticotropin-releasing_hormone) hormone, thus antagonizing IL-1). The suppressor cells are not affected by glucosteroid response-modifying factor (GRMF),[[12]](#cite_note-12) so the effective setpoint for the immune cells may be even higher than the setpoint for physiological processes (reflecting [leukocyte](/wiki/Leukocyte) redistribution to lymph nodes, [bone marrow](/wiki/Bone_marrow), and [skin](/wiki/Skin)). Rapid administration of [corticosterone](/wiki/Corticosterone) (the endogenous Type I and Type II receptor agonist) or [RU28362](/wiki/RU28362) (a specific Type II receptor agonist) to adrenalectomized animals induced changes in [leukocyte](/wiki/Leukocyte) distribution. [Natural killer cells](/wiki/Natural_killer_cell) are affected by cortisol.[[13]](#cite_note-13) Cortisol stimulates many copper enzymes (often to 50% of their total potential), probably to increase copper availability for immune purposes.[[14]](#cite_note-14)[Template:Rp](/wiki/Template:Rp) This includes lysyl oxidase, an enzyme that cross-links collagen and [elastin](/wiki/Elastin).[[14]](#cite_note-14)[Template:Rp](/wiki/Template:Rp) Especially valuable for immune response is cortisol's stimulation of the [superoxide dismutase](/wiki/Superoxide_dismutase),[[15]](#cite_note-15) since this copper enzyme is almost certainly used by the body to permit superoxides to poison bacteria.

## Other effects[[edit](/index.php?title=(none)&action=edit&section=4)]

### Metabolism[[edit](/index.php?title=(none)&action=edit&section=5)]

#### Glucose[[edit](/index.php?title=(none)&action=edit&section=6)]

Cortisol counteracts [insulin](/wiki/Insulin), contributes to hyperglycemia-causing hepatic [gluconeogenesis](/wiki/Gluconeogenesis)[[16]](#cite_note-16) and inhibits the peripheral utilization of glucose ([insulin resistance](/wiki/Insulin_resistance))[[16]](#cite_note-16) by decreasing the translocation of [glucose transporters](/wiki/Glucose_transporter) (especially [GLUT4](/wiki/GLUT4)) to the cell membrane.[[17]](#cite_note-17) However, cortisol increases [glycogen](/wiki/Glycogen) synthesis ([glycogenesis](/wiki/Glycogenesis)) in the [liver](/wiki/Liver).[[18]](#cite_note-18) The permissive effect of cortisol on insulin action in liver glycogenesis is observed in hepatocyte culture in the laboratory, although the mechanism for this is unknown.

#### Bone and collagen[[edit](/index.php?title=(none)&action=edit&section=7)]

Cortisol reduces bone formation,[[2]](#cite_note-2) favoring long-term development of [osteoporosis](/wiki/Osteoporosis) (progressive bone disease). It transports [potassium](/wiki/Potassium) out of cells in exchange for an equal number of [sodium](/wiki/Sodium) ions (see above).[[19]](#cite_note-19) This can trigger the [hyperkalemia](/wiki/Hyperkalemia) of [metabolic shock](/wiki/Shock_(circulatory)#Other_proposed_types_of_shock) from surgery. Cortisol also reduces [calcium](/wiki/Calcium) absorption in the intestine.[[20]](#cite_note-20) [Collagen](/wiki/Collagen) is an important component of connective tissue. It is vital for structural support and is found in muscles, tendons, and joints, as well as throughout the entire body. Cortisol down regulates the synthesis of collagen.[[21]](#cite_note-21)

#### Amino acid[[edit](/index.php?title=(none)&action=edit&section=8)]

Cortisol raises the free amino acids in the serum. It does this by inhibiting collagen formation, decreasing amino acid uptake by muscle, and inhibiting protein synthesis.[[22]](#cite_note-22) Cortisol (as opticortinol) may inversely inhibit [IgA](/wiki/IgA) precursor cells in the intestines of calves.[[23]](#cite_note-23) Cortisol also inhibits IgA in serum, as it does [IgM](/wiki/IgM); however, it is not shown to inhibit [IgE](/wiki/IgE).[[24]](#cite_note-24)

### Wound healing[[edit](/index.php?title=(none)&action=edit&section=9)]

Cortisol and the stress response have known deleterious effects on the immune system. High levels of perceived stress and increases in cortisol have been found to lengthen wound healing time in healthy, male adults. Those who had the lowest levels of cortisol the day following a 4 mm [punch biopsy](/wiki/Punch_biopsy) had the fastest healing time.[[25]](#cite_note-25) In dental students, wounds from punch biopsies took an average of 40% longer to heal when performed three days before an examination as opposed to biopsies performed on the same students during summer vacation.[[26]](#cite_note-26) This is in line with previous animal studies that show similar detrimental effects on wound healing, notably the primary reports showing that turtles recoil from cortisol.[[27]](#cite_note-27)

### Electrolyte and water balance[[edit](/index.php?title=(none)&action=edit&section=10)]

Cortisol acts as a [diuretic](/wiki/Diuretic), increasing water diuresis, glomerular filtration rate, and renal plasma flow from the kidneys, as well as increasing sodium retention and potassium excretion. It also increases sodium and water absorption and potassium excretion in the intestines.[[28]](#cite_note-28)

#### Sodium[[edit](/index.php?title=(none)&action=edit&section=11)]

Cortisol promotes sodium absorption through the small intestine of mammals.[[29]](#cite_note-29) Sodium depletion, however, does not affect cortisol levels[[30]](#cite_note-30) so cortisol cannot be used to regulate serum sodium. Cortisol's original purpose may have been sodium transport. This hypothesis is supported by the fact that freshwater fish utilize cortisol to stimulate sodium inward, while saltwater fish have a cortisol-based system for expelling excess sodium.[[31]](#cite_note-31)

#### Potassium[[edit](/index.php?title=(none)&action=edit&section=12)]

A sodium load augments the intense potassium excretion by cortisol. [Corticosterone](/wiki/Corticosterone) is comparable to cortisol in this case.[[32]](#cite_note-32) For potassium to move out of the cell, cortisol moves an equal number of sodium ions into the cell.[[19]](#cite_note-19) This should make [pH](/wiki/PH) regulation much easier (unlike the normal potassium-deficiency situation, in which two sodium ions move in for each three potassium ions that move out—closer to the [deoxycorticosterone](/wiki/Deoxycorticosterone) effect).

### Gastric and renal secretion[[edit](/index.php?title=(none)&action=edit&section=13)]

Cortisol stimulates gastric-acid secretion.[[33]](#cite_note-33) Cortisol's only direct effect on the hydrogen ion excretion of the kidneys is to stimulate the excretion of ammonium ions by deactivating the renal glutaminase enzyme.[[34]](#cite_note-34)

### Memory[[edit](/index.php?title=(none)&action=edit&section=14)]

Cortisol works with [epinephrine](/wiki/Epinephrine) (adrenaline) to create [memories](/wiki/Memory) of short-term emotional events; this is the proposed mechanism for storage of [flash bulb memories](/wiki/Flash_bulb_memories), and may originate as a means to remember what to avoid in the future.[[35]](#cite_note-35) However, long-term exposure to cortisol damages cells in the [hippocampus](/wiki/Hippocampus);[[36]](#cite_note-36) this damage results in impaired learning. Furthermore, it has been shown that cortisol inhibits memory retrieval of already stored information.[[37]](#cite_note-37)[[38]](#cite_note-38)

### Sleep, stress, and depression[[edit](/index.php?title=(none)&action=edit&section=15)]

[Diurnal](/wiki/Wiktionary:diurnal) cycles of cortisol levels are found in humans.[[5]](#cite_note-5) In humans, the amount of cortisol present in the [blood](/wiki/Blood) undergoes diurnal variation; the level peaks in the early morning (approximately 8 a.m.) and reaches its lowest level at about midnight-4 a.m., or three to five hours after the onset of [sleep](/wiki/Sleep). Information about the [light/dark cycle](/wiki/Circadian_rhythm) is transmitted from the [retina](/wiki/Retina) to the paired [suprachiasmatic nuclei](/wiki/Suprachiasmatic_nuclei) in the [hypothalamus](/wiki/Hypothalamus). This pattern is not present at birth; estimates of when it begins vary from two weeks to nine months of age.[[39]](#cite_note-39) Changed patterns of serum cortisol levels have been observed in connection with abnormal [ACTH](/wiki/ACTH) levels, [clinical depression](/wiki/Clinical_depression), [psychological stress](/wiki/Stress_(biology)), and physiological stressors such as [hypoglycemia](/wiki/Hypoglycemia), illness, [fever](/wiki/Fever), trauma, [surgery](/wiki/Surgery), [fear](/wiki/Fear), [pain](/wiki/Pain), physical exertion, or [temperature](/wiki/Temperature) extremes. Cortisol levels may also differ for individuals with [autism](/wiki/Autism) or [Asperger's syndrome](/wiki/Asperger's_syndrome).[[40]](#cite_note-40) There is also significant individual variation, although a given person tends to have consistent rhythms.[[41]](#cite_note-41)

### Effects during pregnancy[[edit](/index.php?title=(none)&action=edit&section=16)]

During human pregnancy, increased fetal production of cortisol between weeks 30 and 32 initiates production of fetal lung [surfactant](/wiki/Surfactant) to promote maturation of the lungs. In fetal lambs, glucocorticoids (principally cortisol) increase after about day 130, with lung surfactant increasing greatly, in response, by about day 135,[[42]](#cite_note-42) and although lamb fetal cortisol is mostly of maternal origin during the first 122 days, 88 percent or more is of fetal origin by day 136 of gestation.[[43]](#cite_note-43) Although the timing of fetal cortisol concentration elevation in sheep may vary somewhat, it averages about 11.8 days before the onset of labor.[[44]](#cite_note-44) In several livestock species (e.g. the cow, sheep, goat and pig), the surge of fetal cortisol late in gestation triggers the onset of parturition by removing the progesterone block of cervical dilation and [myometrial contraction](/wiki/Myometrium#Excitation-contraction). The mechanisms yielding this effect on progesterone differ among species. In the sheep, where progesterone sufficient for maintaining pregnancy is produced by the placenta after about day 70 of gestation,[[45]](#cite_note-45)[[46]](#cite_note-46) the pre-partum fetal cortisol surge induces placental enzymatic conversion of progesterone to estrogen. (The elevated level of estrogen stimulates prostaglandin secretion and oxytocin receptor development.)

Exposure of fetuses to cortisol during gestation can have a variety of developmental outcomes, including alterations in prenatal and postnatal growth patterns. In marmosets, a species of New World primates, pregnant females have varying levels of cortisol during gestation, both within and between females. Mustoe et al. (2012) showed that infants born to mothers with high gestational cortisol during the first trimester of pregnancy had lower rates of growth in body mass indices (BMI) than infants born to mothers with low gestational cortisol (approximately 20% lower). However, postnatal growth rates in these high-cortisol infants was more rapid than low-cortisol infants later in postnatal periods, and complete catch-up in growth had occurred by 540 days of age. These results suggest that gestational exposure to cortisol in fetuses has important potential fetal programming effects on both pre- and post-natal growth in primates.[[47]](#cite_note-47)

## Synthesis and release[[edit](/index.php?title=(none)&action=edit&section=17)]

Cortisol is produced in the human body by the [adrenal gland](/wiki/Adrenal_gland) in the zona fasciculata,[[48]](#cite_note-48) the second of three layers comprising the [adrenal cortex](/wiki/Adrenal_cortex). The cortex forms the outer "bark" of each adrenal gland, situated atop the kidneys. The release of cortisol is controlled by the [hypothalamus](/wiki/Hypothalamus), a part of the brain. The secretion of [corticotropin-releasing hormone (CRH)](/wiki/Corticotropin-releasing_hormone) by the hypothalamus[[49]](#cite_note-49) triggers cells in the neighboring anterior pituitary to secrete another hormone, the [adrenocorticotropic hormone (ACTH)](/wiki/Adrenocorticotropic_hormone), into the [vascular system](/wiki/Vascular_system), through which blood carries it to the adrenal cortex. ACTH stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and [dehydroepiandrosterone (DHEA)](/wiki/Dehydroepiandrosterone).

[thumb|Cortisol for injection](/wiki/File:Cortisol_for_injection.jpg)

### Normal levels[[edit](/index.php?title=(none)&action=edit&section=18)]

Normal values indicated in the following tables pertain to humans (normals vary among species). Measured cortisol levels, and therefore reference ranges, depend on the analytical method used and factors such as age and sex. Test results should, therefore, always be interpreted using the reference range from the laboratory that produced the result.

|  |  |  |  |
| --- | --- | --- | --- |
| [Reference ranges for blood plasma](/wiki/Reference_ranges_for_blood_plasma) content of free cortisol | | | |
| **Time** | **Lower limit** | **Upper limit** | **Unit** |
| rowspan=2| 09:00 [am](/wiki/Ante_meridiem) | 140<ref name=goodhope>[Biochemistry Reference Ranges at Good Hope Hospital](http://web.archive.org/web/20100720014644/http://www.goodhope.org.uk/Departments/pathweb/refranges.htm) Retrieved 8 November 2009[Template:Better source](/wiki/Template:Better_source)</ref> | 700[[50]](#cite_note-50) | nmol/L |
| 5<ref name=cortisol-derived>Derived from molar values using molar mass of 362 g/mol</ref> | 25[[51]](#cite_note-51) | μg/dL |  |
| rowspan=2| Midnight | 80[[50]](#cite_note-50) | 350[[50]](#cite_note-50) | nmol/L |
| 2.9[[51]](#cite_note-51) | 13[[51]](#cite_note-51) | μg/dL |  |

Using the molecular weight of 362.460 g/mole, the conversion factor from µg/dl to nmol/L is approximately 27.6; thus, 10 µg/dl is approximately equal to 276 nmol/L.

|  |  |  |
| --- | --- | --- |
| [Reference ranges](/wiki/Reference_range) for [urinalysis](/wiki/Urinalysis) of free cortisol | | |
| **Lower limit** | **Upper limit** | **Unit** |
| 28<ref name=cortisol-mass>Converted from µg/24h, using molar mass of 362.460 g/mol</ref> or 30<ref name=Gorges1999>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> | 280[[52]](#cite_note-52) or 490[[53]](#cite_note-53) | [nmol](/wiki/Nanomole)/24h |
| 10[[54]](#cite_note-54) or 11<ref name=cortisol-molar>Converted from nmol/24h, using molar mass of 362.460 g/mol</ref> | 100[[54]](#cite_note-54) or 176[[55]](#cite_note-55) | [µg](/wiki/Microgram)/24 h |

### Disorders of cortisol production[[edit](/index.php?title=(none)&action=edit&section=19)]

* [**Hypercortisolism**](/wiki/Cushing's_syndrome): Excessive levels of cortisol in the blood.
* [**Hypocortisolism**](/wiki/Adrenal_insufficiency): Insufficient levels of cortisol in the blood.

Disorders of cortisol production, and some consequent conditions, are as follows:

* Primary hypercortisolism ([Cushing's syndrome](/wiki/Cushing's_syndrome))
* Primary hypocortisolism ([Addison's disease](/wiki/Addison's_disease), [Nelson's syndrome](/wiki/Nelson's_syndrome))
  + Secondary hypercortisolism (pituitary tumor resulting in [Cushing's disease](/wiki/Cushing's_disease),<ref name=NIH2008>[Template:Cite web](/wiki/Template:Cite_web)</ref>[[56]](#cite_note-56) [pseudo-Cushing's syndrome](/wiki/Pseudo-Cushing's_syndrome))
  + Secondary hypocortisolism (pituitary tumor, [Sheehan's syndrome](/wiki/Sheehan's_syndrome))

## Regulation[[edit](/index.php?title=(none)&action=edit&section=20)]

The primary control of cortisol is the [pituitary](/wiki/Pituitary) gland peptide, adrenocorticotropic hormone ([ACTH](/wiki/ACTH)). ACTH probably controls cortisol by controlling the movement of calcium into the cortisol-secreting target cells.[[57]](#cite_note-57) ACTH is in turn controlled by the hypothalamic peptide [corticotropin-releasing hormone](/wiki/Corticotropin-releasing_hormone) (CRH), which is under nervous control. CRH acts synergistically with [arginine vasopressin](/wiki/Arginine_vasopressin), [angiotensin II](/wiki/Angiotensin_II), and [epinephrine](/wiki/Epinephrine).[[58]](#cite_note-58) (In swine, which do not produce arginine vasopressin, lysine vasopressin acts synergistically with CRH.[[59]](#cite_note-59))

When activated macrophages start to secrete [interleukin-1](/wiki/Interleukin-1) (IL-1), which synergistically with CRH increases ACTH,[[11]](#cite_note-11) [T-cells](/wiki/T-cells) also secrete glucosteroid response modifying factor (GRMF or GAF) as well as IL-1; both increase the amount of cortisol required to inhibit almost all the immune cells.[[12]](#cite_note-12) Immune cells then assume their own regulation, but at a higher cortisol setpoint. The increase in cortisol in diarrheic calves is minimal over healthy calves, however, and falls over time.[[60]](#cite_note-60) The cells do not lose all their fight-or-flight override because of interleukin-1's synergism with CRH. Cortisol even has a negative feedback effect on interleukin-1[[11]](#cite_note-11)—especially useful to treat diseases that force the [hypothalamus](/wiki/Hypothalamus) to secrete too much CRH, such as those caused by endotoxic bacteria. The suppressor immune cells are not affected by GRMF,[[12]](#cite_note-12) so the immune cells' effective setpoint may be even higher than the setpoint for physiological processes. GRMF (known as GAF in this reference) affects primarily the liver (rather than the kidneys) for some physiological processes.[[61]](#cite_note-61) High-potassium media (which stimulates aldosterone secretion in vitro) also stimulate cortisol secretion from the fasciculata zone of canine adrenals [[62]](#cite_note-62)[[63]](#cite_note-63) — unlike [corticosterone](/wiki/Corticosterone), upon which potassium has no effect.[[64]](#cite_note-64) Potassium loading also increases ACTH and cortisol in humans.[[65]](#cite_note-65) This is probably the reason why potassium deficiency causes cortisol to decline (as mentioned) and causes a decrease in conversion of 11-deoxycortisol to cortisol.[[66]](#cite_note-66) This may also have a role in rheumatoid-arthritis pain; cell potassium is always low in RA.[[67]](#cite_note-67)

### Factors reducing cortisol levels[[edit](/index.php?title=(none)&action=edit&section=21)]

* [Magnesium](/wiki/Magnesium) supplementation decreases serum cortisol levels after aerobic exercise,[[68]](#cite_note-68)[[69]](#cite_note-69) but not after resistance training.[[70]](#cite_note-70)\* [Omega-3 fatty acids](/wiki/Omega-3_fatty_acid) have a dose-dependent effect[[71]](#cite_note-71) in slightly reducing cortisol release influenced by mental stress,[[72]](#cite_note-72) suppressing the synthesis of [interleukin](/wiki/Interleukin)-1 and -6 and enhancing the synthesis of interleukin-2; the former promotes higher [CRH](/wiki/Corticotropin-releasing_hormone) release. [Omega-6 fatty acids](/wiki/Omega-6_fatty_acid), on the other hand, have an inverse effect on interleukin synthesis.[[73]](#cite_note-73)\* [Music therapy](/wiki/Music_therapy) can reduce cortisol levels in certain situations.[[74]](#cite_note-74)\* [Massage therapy](/wiki/Massage_therapy) can reduce cortisol.[[75]](#cite_note-75)\* Laughing, and the experience of humour, can lower cortisol levels.[[76]](#cite_note-76)\* Soy-derived [phosphatidylserine](/wiki/Phosphatidylserine) interacts with cortisol; the correct dose, however, is unclear.[[77]](#cite_note-77)[[78]](#cite_note-78)[[79]](#cite_note-79)<ref name=medicalnewstoday>[Template:Cite web](/wiki/Template:Cite_web)</ref>
* Regular dancing has been shown to lead to significant decreases in salivary cortisol concentrations.<ref name=Quiroga\_2009>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>
* [Withania somnifera](/wiki/Withania_somnifera) (Ashwagandha) root extract.[[80]](#cite_note-80)

### Factors increasing cortisol levels[[edit](/index.php?title=(none)&action=edit&section=22)]

* Viral infections increase cortisol levels through activation of the HPA axis by cytokines.[[81]](#cite_note-81)\* [Caffeine](/wiki/Caffeine) may increase cortisol levels.[[82]](#cite_note-82)\* [Sleep deprivation](/wiki/Sleep_deprivation)[[83]](#cite_note-83)\* Intense (high [VO2 max](/wiki/VO2_max)) or prolonged [aerobic exercise](/wiki/Aerobic_exercise) transiently increases cortisol levels to increase gluconeogenesis and maintain blood glucose;[[84]](#cite_note-84) however, cortisol declines to normal levels after eating (i.e., restoring a neutral [energy balance](/wiki/Energy_balance_(biology)))[[85]](#cite_note-85)\* The Val/Val variation of the [BDNF](/wiki/BDNF) gene in men and the Val/Met variation in women are associated with increased salivary cortisol in a stressful situation.[[86]](#cite_note-86)\* [Hypoestrogenism](/wiki/Hypoestrogenism) and [melatonin](/wiki/Melatonin) supplementation increase cortisol levels in postmenopausal women.[[87]](#cite_note-87)\* Severe trauma or stressful events can elevate cortisol levels in the blood for prolonged periods.[[88]](#cite_note-88)\* Subcutaneous adipose tissue regenerates cortisol from [cortisone](/wiki/Cortisone) by the enzyme [11-beta HSD1](/wiki/11β-hydroxysteroid_dehydrogenase_type_1).[[89]](#cite_note-89)\* [Anorexia nervosa](/wiki/Anorexia_nervosa) may be associated with increased cortisol levels.[[90]](#cite_note-90)\* The [serotonin](/wiki/Serotonin) receptor gene [5HTR2C](/wiki/5-HT2C_receptor) is associated with increased cortisol production in men.[[91]](#cite_note-91)\* Posing in low-power nonverbal displays through close, contractive postures can increase cortisol levels.[[92]](#cite_note-92)\* Smelling [androstadienone](/wiki/Androstadienone) has been found in one study to raise cortisol levels in women; as well as, in other studies, to affect mood (see [androstadienone](/wiki/Androstadienone) article for details and citations).

## Pharmacology[[edit](/index.php?title=(none)&action=edit&section=23)]

Hydrocortisone is the pharmaceutical term for cortisol used in oral administration, intravenous injection, or topical application. It is used as an [immunosuppressive drug](/wiki/Immunosuppressive_drug), given by injection in the treatment of severe allergic reactions such as [anaphylaxis](/wiki/Anaphylaxis) and [angioedema](/wiki/Angioedema), in place of [prednisolone](/wiki/Prednisolone) in patients needing steroid treatment but unable take oral medication, and perioperatively in patients on long-term steroid treatment to prevent [Addisonian crisis](/wiki/Addison's_disease). It may also be injected into inflamed joints resulting from diseases such as [gout](/wiki/Gout).

Compared to hydrocortisone, [prednisolone](/wiki/Prednisolone) is about four times as strong and [dexamethasone](/wiki/Dexamethasone) about forty times as strong, in their [anti-inflammatory](/wiki/Anti-inflammatory) effect.<ref name=Dexamethasone>[Template:Cite web](/wiki/Template:Cite_web)</ref> Prednisolone can also be used as cortisol replacement, and at replacement dose levels (rather than anti-inflammatory levels), prednisolone is about eight times more potent than cortisol.[[93]](#cite_note-93) For side effects, see [corticosteroid](/wiki/Corticosteroid) and [prednisolone](/wiki/Prednisolone).

It may be used topically for allergic rashes, [eczema](/wiki/Eczema), [psoriasis](/wiki/Psoriasis), [pruritis](/wiki/Pruritis) (itchyness) and other inflammatory skin conditions. Topical hydrocortisone creams and ointments are available in most countries without prescription in strengths ranging from 0.05% to 2.5% (depending on local regulations) with stronger forms available by prescription only. Covering the skin after application increases the absorption and effect. Such enhancement is sometimes prescribed, but otherwise should be avoided to prevent overdose and systemic impact.

### Protein binding[[edit](/index.php?title=(none)&action=edit&section=24)]

Most serum cortisol (all but about 4%) is bound to proteins, including [corticosteroid binding globulin](/wiki/Transcortin) (CBG) and [serum albumin](/wiki/Serum_albumin). Free cortisol passes easily through cellular membranes, where they bind intracellular [cortisol receptors](/wiki/Cortisol_receptor).[[94]](#cite_note-94)

## Biochemistry[[edit](/index.php?title=(none)&action=edit&section=25)]

### Biosynthesis[[edit](/index.php?title=(none)&action=edit&section=26)]

[thumb|right|400px|](/wiki/File:Steroidogenesis.svg)[Steroidogenesis](/wiki/Steroidogenesis), showing cortisol at right.

Cortisol is synthesized from [cholesterol](/wiki/Cholesterol). Synthesis takes place in the [*zona fasciculata*](/wiki/Zona_fasciculata) of the [adrenal cortex](/wiki/Adrenal_cortex). (The name *cortisol* is derived from *cortex*.) While the adrenal cortex also produces [aldosterone](/wiki/Aldosterone) (in the *zona glomerulosa*) and some [sex hormones](/wiki/Sex_hormone) (in the *zona reticularis*), cortisol is its main secretion in humans and several other species. (However, in cattle, corticosterone levels may approach[[95]](#cite_note-95) or exceed[[5]](#cite_note-5) cortisol levels.). The medulla of the adrenal gland lies under the cortex, mainly secreting the catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine) under sympathetic stimulation.

The synthesis of cortisol in the adrenal gland is stimulated by the [anterior lobe](/wiki/Anterior_pituitary) of the [pituitary gland](/wiki/Pituitary_gland) with [adrenocorticotropic hormone](/wiki/Adrenocorticotropic_hormone) (ACTH); ACTH production is in turn stimulated by [corticotropin-releasing hormone](/wiki/Corticotropin-releasing_hormone) (CRH), which is released by the [hypothalamus](/wiki/Hypothalamus). ACTH increases the concentration of cholesterol in the inner mitochondrial membrane, via regulation of the STAR (steroidogenic acute regulatory) protein. It also stimulates the main rate-limiting step in cortisol synthesis, in which cholesterol is converted to pregnenolone and catalyzed by Cytochrome P450SCC ([side-chain cleavage enzyme](/wiki/Side-chain_cleavage_enzyme)).[[96]](#cite_note-96)

### Metabolism[[edit](/index.php?title=(none)&action=edit&section=27)]

Cortisol is metabolized by the [11-beta hydroxysteroid dehydrogenase](/wiki/11-beta_hydroxysteroid_dehydrogenase) system (11-beta HSD), which consists of two enzymes: [11-beta HSD1](/wiki/11-beta_HSD1) and [11-beta HSD2](/wiki/11-beta_HSD2).

* *11-beta HSD1* utilizes the cofactor NADPH to convert biologically inert [cortisone](/wiki/Cortisone) to biologically active cortisol
* *11-beta HSD2* utilizes the cofactor NAD+ to convert cortisol to cortisone

Overall, the net effect is that 11-beta HSD1 serves to increase the local concentrations of biologically active cortisol in a given tissue; 11-beta HSD2 serves to decrease local concentrations of biologically active cortisol.

Cortisol is also metabolized into 5-alpha tetrahydrocortisol (5-alpha THF) and 5-beta tetrahydrocortisol (5-beta THF), reactions for which [5-alpha reductase](/wiki/5-alpha_reductase) and 5-beta reductase are the [rate-limiting factors](/wiki/Rate-determining_step), respectively. 5-Beta reductase is also the rate-limiting factor in the conversion of cortisone to [tetrahydrocortisone](/wiki/Tetrahydrocortisone) (THE).

An alteration in [11-beta HSD1](/wiki/11β-hydroxysteroid_dehydrogenase_type_1) has been suggested to play a role in the [pathogenesis](/wiki/Pathogenesis) of [obesity](/wiki/Obesity), [hypertension](/wiki/Hypertension), and [insulin resistance](/wiki/Insulin_resistance) known as [metabolic syndrome](/wiki/Metabolic_syndrome).[[97]](#cite_note-97) An alteration in [11-beta HSD2](/wiki/Corticosteroid_11-beta-dehydrogenase_isozyme_2) has been implicated in [essential hypertension](/wiki/Essential_hypertension) and is known to lead to the [syndrome of apparent mineralocorticoid excess](/wiki/Syndrome_of_apparent_mineralocorticoid_excess) (SAME).

## See also[[edit](/index.php?title=(none)&action=edit&section=28)]

* [Cortisone](/wiki/Cortisone), a hormone
* [Cortizone](/wiki/Cortizone), a medication
* [Membrane glucocorticoid receptor](/wiki/Membrane_glucocorticoid_receptor)

## References[[edit](/index.php?title=(none)&action=edit&section=29)]

[Template:Reflist](/wiki/Template:Reflist)

## External links[[edit](/index.php?title=(none)&action=edit&section=30)]

[Template:Commons category](/wiki/Template:Commons_category)

* [Cortisol MS Spectrum](http://gmd.mpimp-golm.mpg.de/Spectrums/925c5612-4ecd-461b-bb52-173189b86299.aspx)
* [Dosage Side Effects and Drug Interaction Warnings](http://arthritis.about.com/od/hydrocortisone/Hydrocortisone_Dosage_Side_Effects_Drug_Interactions_Warnings.htm)
* Cortisol (serum/plasma) at [Lab Tests Online](http://labtestsonline.org/understanding/analytes/cortisol/tab/test)
* [Cortisol: analyte monograph](http://www.acb.org.uk/docs/NHLM/Cortisol.pdf) – The Association for Clinical Biochemistry and Laboratory Medicine
* [How to stay healthy with Cortisol](http://stress.about.com/od/stresshealth/a/cortisol.htm)

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