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COMMENTARY

GLUCOCORTICOID–BIOGENIC AMINE INTERACTIONS IN RELATION TO MOOD AND BEHAVIOR

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Adrenal glucocorticoids are linked to nervous system function in disparate ways, involving actions on the sympathetic nervous system in relation to stress and traumatic shock [1] as well as effects that alter mood and trigger psychosis [2]. In these and other actions, there is strong reason to suspect an interaction between glucocorticoids and biogenic amines.

Due to recent advances in the study of steroid actions in the nervous system and in our knowledge of neurotransmitters, we are beginning to find out a great deal about how glucocorticoids and other steroid hormones affect the process of neurotransmission. Glucocorticoid effects are often discretely localized within the nervous system and differ among brain structures. They involve genomic actions of the steroid in some cases and direct membrane actions in others. And they occur during development, in mature functioning of neural tissue, and in relation to the aging process. This article examines the impact of glucocorticoids on the brain, placing particular emphasis on the interactions between glucocorticoids and biogenic amines, such as serotonin, dopamine and epinephrine, and their effects on mood and on behavior.

Glucocorticoids, mood and mental state

The importance of glucocorticoid actions on the central nervous system is highlighted by the effects of these hormones on mood and mental activity. Endogenous depressive illness has been linked to abnormalities in pituitary–adrenal function [3] and to resistance to dexamethasone suppression in the "dexamethasone suppression test" (DST) [4, 5]. Endogenous depressive illness is heterogenous and has been subtyped; higher incidences of abnormal DSTs have been identified in familial pure depressive disease, compared to sporadic depressive disease and depression spectrum disease [6]. Furthermore, in keeping with the original work of Sachar *et al.* [3], which identified abnormal cortisol secretion in psychotic depression, patients with this trait are also recognized as having a high incidence of abnormal DSTs [7–9]. In this connection, it is important to note that one of the frequent side-effects of elevated glucocorticoid levels is psychotic episodes [2], and elevations in dopamine metabolism are linked to glucocorticoid elevation (see below).

An abnormal DST, encountered in many endogenously depressed patients, is also found in normal individuals who have experienced a recent stressful period [10]. Abnormal DSTs are also encountered in chronic alcoholics [11] and in mentally-retarded [12] and schizophrenic [10] individuals. As such, the DST may be a state marker of persistent recent stress rather than a specific trait marker of disease. In this case, one may ask whether, in depressed subjects, glucocorticoid elevation contributes in any way to the symptoms of depression. In fact, stress is a recognized factor in precipitating depression [13], although the causal role of the steroid component of stress is far from clear. Nevertheless, glucocorticoids do contribute by enhancing some of the traits associated with depressive illness. Exogenous glucocorticoids modestly increase anxiety in normal subjects [14], and Cushing's syndrome has been linked to a high incidence of depression [15, 16]. In Cushing's patients, who have elevated glucocorticoid levels, relief of the depressed affect occurred over several weeks or months after the tumor or hyperplastic tissue was removed [15].

Overdosage with glucocorticoids leads to euphoria, hyperactivity, increased appetite, sleeplessness, and sometimes to tension, irritability and psychotic episodes. In general, such effects of elevated glucocorticoids are also seen in Cushing's syndrome as well as after giving high levels of glucocorticoids to either normal or hypoadrenocortical patients [2]. Thus, adrenal steroid excess promotes traits recognized in depressive illness, such as anxiety, agitation, dysphoria, sleeplessness and psychotic episodes. In spite of these rather straightforward relationships, the connection between adrenal steroids and mood is not a simple one [2]. For example, hypoadrenocorticism is associated with apathy, depression, dysphoria and memory impairment, and glucocorticoid therapy is generally effective in correcting these symptoms whereas mineralocorticoids seldom cause mental effects [2]. In other words, there is some resemblance between the symptoms of hyper- and hypoadrenocorticism, as if there is a U-shaped dose–response curve for some of the behavioral features. This is puzzling. Moreover, another puzzle is that depression and adrenocortical hormone elevation are dissociable, at least for periods of time, and significant numbers of endogenously depressed patients have normal DSTs. Clearly, adrenal glucocorticoids are only one of the contributing biochemical factors to depressed affect, and they may exacerbate imbalances which are already present in susceptible individuals. In view of the importance of biogenic amine disturbances in depressive illness, we may seek clues to such interactions

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in the effects of glucocorticoids on biogenic amine systems.

Glucocorticoid effects on biogenic amines

Because biogenic amines are implicated in normal and abnormal mental states, they may be involved, at least in part, in glucocorticoid influences on mood and behavior. Using this as a starting point, it has been possible to uncover a variety of interactions between glucocorticoids and principal biogenic amine systems. In this section, we shall consider those interactions which are most relevant to the mood and behavior-related effects of glucocorticoids discussed above.

Serotonin. Serotonin is associated with the level of fear displayed by a rat, and both fear and serotonin turnover are influenced by adrenal secretions. Elevation of serotonin levels in the rat brain reduces fear, whereas reduction of serotonin levels or blockade of its actions increases fear [17]. Adrenalectomy (ADX) increases fear in rats [18], and it also decreases indices of serotonin metabolism in hippocampus, hypothalamus and midbrain [19–22]. Further indications that adrenal steroids increase serotonin metabolism are that inhibition of adrenal steroid biosynthesis decreases hippocampal serotonin levels [23] and that ADX decreases the *in vivo* conversion index of tryptophan to serotonin in rat forebrain and brainstem [24], as well as decreasing serotonin formation in homogenates of forebrain tissue [25].

Stressful procedures such as restraint of rats causes serotonin turnover to increase [26–29]. Activity of the rate-limiting serotonin biosynthetic enzyme, tryptophan hydroxylase, increases following a variety of stresses [30, 31]; and these increases in response to stress are reduced markedly in ADX rats [31], suggesting that the glucocorticoids play a "permissive" role in the actions of stress.

The reduction of serotonin turnover after ADX occurs rapidly, within the first hour [32, 33], and is correlated with a phasic increase in pituitary ACTH release [32]. Pargyline-induced accumulation of serotonin is reduced both in the midbrain raphe, the cell body region, and in serotonin projection areas such as the hippocampus [33], although after ADX serotonin levels do not decrease as rapidly as turnover. Corticosterone replacement at the time of ADX prevents the decline [33, 34].

The responsiveness of the serotonin system to glucocorticoids is further indicated by changes in density of serotonin-1 receptors after ADX and corticosterone replacement. One hour after ADX, the serotonin receptor density, measured by quantitative autoradiography, is increased in subiculum, in the molecular layer of the dentate gyrus, and in the dorsal raphe nucleus; corticosterone replacement at the time of ADX reduces serotonin-1 receptor density in hippocampal CA1 field, in dentate gyrus and in dorsal raphe, compared to untreated ADX rats [35]. The corticosterone effect is specific, in that aldosterone does not mimic corticosterone, and changes in serotonin-1 receptors are not observed in cerebral cortex, the CA3 field of hippocampus or in medial raphe [35]. After 6 days of ADX, increased serotonin-1 receptor binding was found in the CA1 field of hippocampus, and this increase is reversed by corticosterone replacement therapy [36]. The effect of short-term manipulations is, therefore, more extensive than the long-term effect of ADX, and one can only speculate that short-term changes in receptors may be secondary to changes in serotonin turnover occurring after ADX and corticosterone treatment, i.e. involving receptor up-regulation after ADX and involving down-regulation following corticosterone-induced increases of serotonin turnover. It is not known whether the longer-term effects of adrenal glucocorticoids are due to the same mechanism or to another action. Consistent with the notion of a glucocorticoid suppression of serotonin receptors is the observation that repeated injections of cortisol to guinea pigs reduces myoclonus elicited by administration of 5-hydroxytryptophan [37].

In conclusion, glucocorticoids have a permissive role in the activation of serotonin formation under stress; however, they also dampen and reduce CNS sensitivity to serotonin which tends to be increased by stress independently of the adrenal influence [38, 39].

Noradrenaline. Thie hippocampus and cerebral cortex receive major input of noradrenergic innervation from the locus coeruleus [40]. Noradrenergic influences on hippocampal neuronal excitability involve a reduction in spontaneous activity and an increase in efficacy of inputs, i.e. by a state of "quite readiness" leading to an enhanced "signal-to-noise" ration [41]. From a behavioral standpoint, this input is implicated in the control of vigilance and in the initiation of adaptive behavioral responses [42]. Lesions of the dorsal noradrenergic bundle, which innervates the hippocampus and cortex, lead to resistance to extinction of appetitively and aversively-motivated operant tasks and of a classically conditioned response [43–45].

Glucocorticoids also influence extinction of learned avoidance behavior as well as extension of an appetitively-motivated task [46–48]. In fact, rats with combined adrenalectomy and dorsal adrenergic bundle lesions are also deficient in acquiring avoidance responses [49–51]. Moreover, a dorsal bundle lesion combined with ADX leads to increased hippocampal β-adrenergic receptor binding [52]. Although the elevated β-receptors may have no function in the absence of endogenous noradrenaline, one may wonder about circulating catecholamines which are generally thought not to cross the blood–brain barrier. However, 48 hr after ADX, with the dorsal bundle intact, rats show retention deficits in passive avoidance which are reversed by subcutaneous administration of exogenous adrenaline [53]. Glucocorticoids influence this process in that corticosterone treatment of ADX rats shifts the dose–response curve toward higher doses, i.e. decreases sensitivity. Such a decrease in sensitivity may be a reflection of the ability of glucocorticoids to reduce noradrenaline-stimulated cyclic AMP generation [54–56].

One of the specific influences of noradrenaline in the hippocampus is to enhance long-term potentiation (LTP) [57–59]. LTP is most pronounced in hippocampus, although it is found throughout the

rat limbic forebrain [60], and it appears to function as a catalyst for learning [61, 62]. Adrenal glucocorticoids, which peak during the end of sleep, regulate the magnitude of LTP, causing it to increase during the waking hours [63, 64]. The effect of glucocorticoids to increase synaptic efficacy, which has been known for some time [65], may thus concern hippocampal sensitivity to noradrenergic input.

Stimuli which evoke LTP can also lead to kindling of seizures when they are repeated, and it has been proposed that a common path may be involved [60]. However, noradrenaline, which facilitates LTP, suppresses kindling [66, 67]. Moreover, ADX protects rats from developing amnesia as a result of kindling [68]. A possible connection is the fact that ADX increases the sensitivity of noradrenaline stimulation of cyclic AMP formation (see below) and may thus increase the protective effects of endogenous noradrenaline. The effects of ADX and corticosterone replacement on kindling are complex and time dependent [69–71], suggesting that pituitary–adrenal hormones influence processes which have multiple influences on neuronal activity underlying kindling.

A principal effect of glucocorticoids on the noradrenergic system is the suppression of noradrenaline-stimulated cAMP formation. This effect has been reported for cerebral cortex [35, 54] and for hippocampus [56]. It is not known how widespread this influence is beyond these two structures. The suppression is also produced by ACTH administration and appears to operate via the α-adrenergic component which influences cAMP generation [72]. Effects of repeated ACTH or corticosterone administration on cAMP generation mimic effects of repeated restraint stress [73], chronically-intermittent food deprivation [73, 74], as well as reduced noradrenaline-stimulated cAMP formation [75].

Another example of glucocorticoid actions affecting sensitivity to noradrenaline is the modulation of α_2-adrenergic receptors in the paraventricular nuclei (PVN) of the hypothalamus in relation to feeding behavior and appetite. In contrast to the cAMP story in cortex and hippocampus, the glucocorticoid effect in the PVN increases sensitivity, i.e. ADX results in a region-specific decline in α_2-adrenergic receptor binding in PVN that is restored by corticosterone replacement; α_1-adrenergic receptor binding is unaffected [76]. Moreover, α_2-receptor binding in PVN peaks at the same time as the peak of corticosterone secretion, suggesting that there may be a relatively rapid modulation of receptors by the hormone [77]. These observations appear to be related to the finding that feeding elicited by noradrenaline injection into the PVN is dependent on circulating corticosterone [78–80].

Glucocorticoids affect other components of the noradrenergic system, although these effects are not always easy to fit into a global view of hormone action in relation to behavior. As is the case for tryptophan and serotonin, glucocorticoid treatment elevates brain tyrosine levels [81] and increases formation of [^{3}H]noradrenaline from [^{3}H]tyrosine [82], but it does not alter tyrosine hydroxylase (TOH) activity in the mature locus coeruleus [83]. However, Kizer *et al.* [84] showed increased TOH activity in median eminence 1 week after ADX which is reversed by dexamethasone, and Van Loon *et al.* [85] demonstrated increased TOH activity after hypophysectomy in hypothalamus which is reversed by ACTH and by dexamethasone. In contrast to TOH, dopamine beta hydroxylase activity in hypothalamus is decreased by hypophysectomy, and this decline is prevented by ACTH treatment [85]. Corticosterone treatment increases hypothalamic dopamine beta hydroxylase activity after it is decreased 2 days following ADX [86].

Thus, glucocorticoids increase conversion of tyrosine to noradrenaline, whereas tyrosine hydroxylase activity is not regulated by glucocorticoids in adult CNS, except in hypothalamus where they reduce it; dopamine beta hydroxylase activity in hypothalamus is stimulated by glucocorticoids. What is the net result for noradrenaline turnover? ADX has been reported to increase noradrenaline turnover, but only after 6 days [87]. On the other hand, another study reports that 1 hr post-ADX, noradrenaline turnover is increased in hypothalamic nuclei, whereas it is decreased in these same areas at longer times after ADX [88]. There is also a peculiarity about the effects of ADX and of stress: both ADX and stress appear to increase noradrenaline turnover, at least in hypothalamus [89–91]; and the effects of ADX on noradrenaline levels or turnover are reversed by glucocorticoid replacement [90, 92]. It is therefore possible that glucocorticoids exert influences on the noradrenergic system which oppose the effects of stress just as appears to be the case for glucocorticoids and CNS serotonin sensitivity (see above).

A discussion of the glucocorticoid–adrenergic interaction would be incomplete without mentioning the autonomic nervous system, where many of the original questions about such interactions were first posed [1]. Tyrosine hydroxylase activity is positively regulated by glucocorticoids in sympathetic ganglia, in that dexamethasone induces an increase in TOH in adrenally-intact rats by a mechanism requiring intact afferent innervation of the ganglion at least up to 24 hr before steroid treatment [93–95]. One peculiar feature of this effect is that, although dexamethasone is a potent inducer, the natural glucocorticoid, corticosterone, and another synthetic steroid, triamcinolone, are ineffective. This has led to the suggestion that a nonclassical presynaptic, membrane action may be involved [95]. Whatever the mechanism, the phenomenon may explain the finding that 10 days of dexamethasone treatment causes a doubling of noradrenaline and dopamine levels in rat carotid body [96, 97].

Epinephrine. Hypophysectomy reduces epinephrine levels and decreases phenylethanolamine *N*-methyl transferase (PNMT) activity in adrenal medulla [98, 99]. Glucocorticoids maintain PNMT activity, which would otherwise decline, in cultures of bovine adrenal medulla [100]. However, stress of adrenally-intact rats for 30 min elevates brainstem, but not adrenal, PNMT activity [101], whereas dexamethasone treatment over a much longer period, namely 6–13 days elevates PNMT in hypothalamus and pons-medulla in both newborn and adult rats [102]. For PNMT, *S*-adenosylmethionine (SAM) serves as a methyl donor, and SAM levels are

decreased by hypophysectomy and restored by dexamethasone in the adrenal medulla, pineal gland, corpus striatum and midbrain; SAM levels increase after hypophysectomy and are not affected by dexamethasone treatment in thalamus, hypothalamus, hippocampus and cerebellum [103].

Dopamine. Glucocorticoids affect dopamine (DA) metabolism in brain. In rats, dexamethasone rapidly increases DA levels in spinal cord [104] and carotid body [97], and increase DA turnover in mouse brain [82]. Dexamethasone treatment increases DA levels in rat hypothalamus and nucleus accumbens, but not in striatum or frontal cortex [105]. In human subjects, plasma-free DA levels are increased markedly after 1 mg of dexamethasone [105]. DA activity which is elevated by glucocorticoids may participate in the symptoms of depression, psychosis or mania which sometimes result from endogenously elevated glucocorticoids [2, 105]. Elevated glucocorticoid levels and reduced dexamethasone suppressibility are linked strongly to unipolar psychotic depression [106].

Conclusions. The overall impression of the evidence regarding glucocorticoid–biogenic amine interactions in the mature nervous system is that the hormonal influence is biphasic. On the one hand, glucocorticoids acutely elevate serotonin, noradrenaline and, possibly also, dopamine formation, and they appear to maintain PNMT activity in adrenal medulla and brainstem as well as dopamine beta hydroxylase activity in hypothalamus. They also increase TOH activity in the autonomic nervous system. On the other hand, over a period of days, glucocorticoids reduce cerebral cortical and hippocampal sensitivity to noradrenaline, and they have a dampening influence on sensitivity to serotonin which opposes the neural effects of stress. Clearly, there is much more to be learned about what is apparently a complicated story involving, to some extent, brain region specific effects of glucocorticoids. However, there is enough information to tentatively suggest that glucocorticoids first potentiate activation of the biogenic amine response to stress and behavioral arousal and then help the nervous system to oppose the neural actions of this stress and arousal which might be deleterious. In this manner, glucocorticoids help to restore the homeostatic balance.

Developmental actions of glucocorticoids in neural tissue

Glucocorticoids influence development of monoaminergic systems in neural tissues, and this review would be incomplete without a brief account of this important area. Although having no effect on tryptophan hydroxylase enzyme amount in adult brain, glucocorticoids are required for the normal developmental rise of this enzyme [107]. Moreover, lesion-induced homotypical sprouting of serotonin axons in hippocampus is depressed by ADX and facilitated by corticosterone [108], suggesting that developmental programs may be reactivated after neural damage.

The developmental story for noradrenaline in locus coeruleus is similar, in that administration of corticosterone during a sensitive period in the second week of postnatal life elevates TOH activity by a process which is blocked by two antiglucocorticoids, progesterone and cortexolone [83]. Moreover, glucocorticoids potentiate the development of the adrenergic phenotype in autonomic nervous system tissue [109–111], and at the same time they suppress expression of the cholinergic phenotype [112–114]. In tissue culture, it has been shown that sympathetic neurons respond to conditioned medium from non-neuronal cells in showing cholinergic or adrenergic differentiation; they do not appear to respond to glucocorticoids directly, but rather the production of factors in conditioned medium which determine cholinergic differentiation is decreased by cortisol and increased by epidermal growth factor [114].

Other developmental effects of glucocorticoids on catechoaminergic neurons are seen in tissue culture, as well as *in vivo*. Glucocorticoids act synergistically with nerve growth factor on TOH induction in superior cervical ganglion [115]. Glucocorticoids also increase the number of small, intensely-fluorescent (SIF) cells, presumably epinephrine-producing, in neural-crest derived tissue and also increase PNMT activity [116].

In conclusion, glucocorticoids promote the development and expression of the serotonergic and catecholaminergic phenotypes and may also potentiate regenerative responses in these neurons. These developmental actions thus complement the activational influences in the mature nervous system by which glucocorticoids potentiate the ability of stress and behavioral arousal to turn on the monoaminergic systems and then dampen their effects.

Mechanisms of glucocorticoid action in neural tissue

Steroid hormones act through intracellular receptor sites which alter genomic activity and increase or decrease levels of specific gene products [117]. At the same time, steroids also affect membrane properties more directly [118–122]. These two possibilities are represented in Fig. 1. Which mechanism is involved in the effects described above?

One way of distinguishing between membrane and genomic effects is by their time courses [123]. Direct effects are rapid in onset and last as long as the steroid is present. Genomic effects do not occur at once, and once they occur they may outlast the presence of steroid in the tissue. Genomic activation and RNA synthesis may occur very rapidly after steroid administration, and the shortest onset latency for steroid effects which can be detected at the level of cell function is on the order of 20 min [124].

Many of the glucocorticoid effects on monoamine systems that have been described above are too complex to have been sorted out as to their mechanisms. Indeed, behavioral effects may reflect the actions of hormones in multiple brain sites via different neurotransmitters and via both membrane and genomic mechanisms. Let us examine some of the more discrete biochemical effects of glucocorticoids on individual monoamine systems, described above, for clues as to underlying mechanisms. The permissive action of corticosterone to allow stress to increase serotonin formation appears to be an example of a membrane effect. In the first place, it occurs rapidly in conjunction with elevated corticosterone

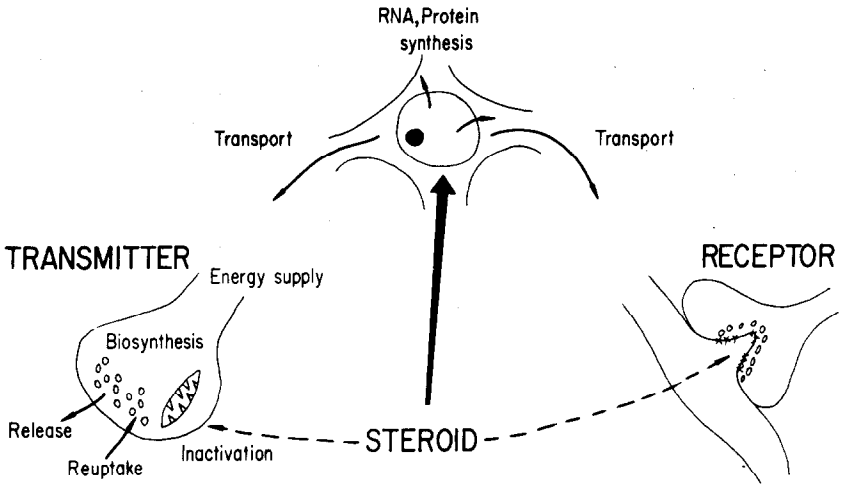

Fig. 1. Steroid hormone effects on neurochemistry. Steroid hormones affect neuronal function via the genome by increasing or decreasing expression of gene products associated with neurotransmission, including biosynthesis and degradation of neurotransmitters, receptors and transport mechanisms, as well as energy metabolism. Effects are discrete both with respect to brain region and gene product affected. Steroids also have direct effects on membranes which influence neurotransmission and electrical activity. These effects are also discrete with respect to brain region and endpoint affected. (From ref. 123 with permission.)

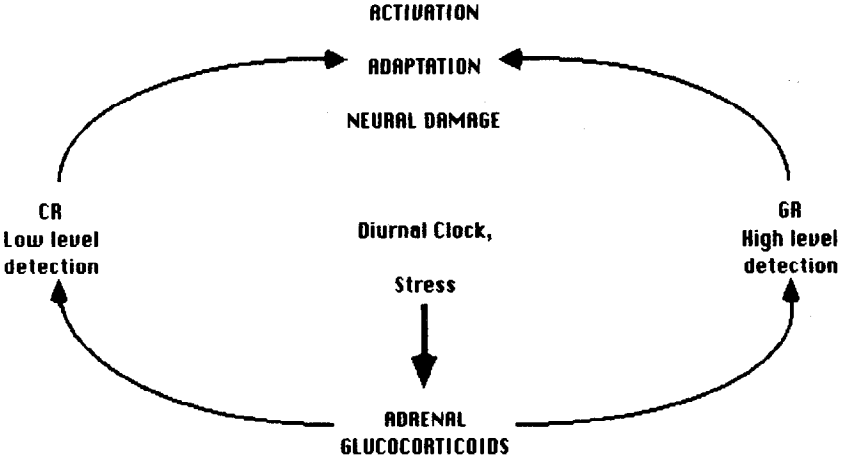

Fig. 2. Glucocorticoid actions through two receptors in brain. Glucocorticoid affect three phases of neural function, referred to as "activation", "adaptation" and "neural damage" (see text), by acting through two receptor subtypes. The corticosterone receptor (CR) is a detector of low levels of corticosterone, whereas the glucocorticoid receptor (GR) is a detector of higher corticosterone levels such as are achieved during stress. CR is found mainly in hippocampus, whereas GR is distributed throughout the brain.

levels and falls rapidly as the hormone level falls, and it occurs concurrently in cell body and terminal regions [31, 125]. Second, corticosterone induces a rapid elevation of tryptophan uptake by nerve endings [126–128] and this may be sufficient to induce an increased serotonin formation, although there is also a corticosterone-induced increase of calcium uptake by nerve endings [129], which could work in parallel with increased substrate through activation of tryptophan hydroxylase catalytic activity [130]. What is not explained in this scheme is why protein synthesis inhibitors such as cycloheximide and puromycin are able to block the corticosterone effect on tryptophan hydroxylase activity [25, 125]. It is possible that the hydroxylation system is sensitive to these inhibitors independently of their ability to block protein synthesis; alternatively, some rapidly turning-over locally-produced protein modulator may be involved [125].

Another rapid effect of glucocorticoids is the increase of α_2-adrenergic receptors in PVN and the consequent increase of food intake induced by noradrenaline (see above). The corticosterone effect to elevate noradrenaline-induced feeding requires a minimum of 15 min, which is no faster than the genomically-mediated actions of corticosterone on thymus lymphocytes [124]. Furthermore, the PVN has intracellular glucocorticoid receptors of the type which mediate genomic steroid actions [131]. Therefore, it is impossible to say on the basis of time course

alone which type of mechanism is involved; possibly, experiments with RNA and protein synthesis inhibitors may allow some resolution of the question.

As far as other effects of glucocorticoids described above, the mechanism is unknown. From what is known about time course, most of them could be mediated by genomic mechanisms. Indeed, the locus coeruleus, as well as raphe nuclei and epinephrine containing cell groups, C1 and C2, of the brainstem contain intracellular glucocorticoid receptors of the type which mediate genomic actions [132–134]. Moreover, the hippocampus, in which many glucocorticoid effects have been found, has the highest concentration of intracellular glucocorticoid receptors of any brain area [134].

Three apsects of glucocorticoid action in brain: Activation, adaptation and neural damage

Intracellular glucocorticoid receptors in brain are classified into two types: Type I, or corticosterone receptors (CR); and Type II, or glucocorticoid receptors (GR) [134]. Type I receptors, or CR, are similar to so-called "mineralocorticoid receptors" in the kidney, whereas Type II receptors, or GR, resemble the classical glucocorticoid receptor of the liver and kidney [135]. The CR system of the brain appears to have a dual role: in the hippocampus and septum, it recognizes corticosterone over aldosterone, but in other brain areas it recognizes aldosterone preferentially over corticosterone [134]. The distinction between CR and GR is intended to emphasize the fact that the CR in brain areas such as hippocampus and septum recognizes corticosterone and functions as a detector for corticosterone levels during the diurnal cycle, whereas the GR recognizes higher levels of circulating corticosterone and also binds synthetic glucocorticoids such as dexamethasone [134, 136, 137] (see Fig. 2). Thus, the GR is a receptor especially well suited to detect and respond to stress-induced changes in corticosterone secretion. The two receptor subtypes are distributed differently within the nervous system [131, 133, 136]. The CR is found in high levels within the hippocampal formation, and to a lesser extent in septum and amygdala, where it is responsible for the dramatic neuronal concentration of [^{3}H]corticosterone *in vivo* [134]. The GR is found in neurons and glial cells and is more widely distributed within the nervous system, occurring not only in hippocampus but also in PVN and in major monoaminergic cell body regions of the brain stem and midbrain [131–133].

The recognition that there are two types of glucocorticoid receptors responding to different levels of hormone has led to the realization that glucocorticoid effects can be divided into three phases depending on the time course and level of hormone secretion. The three phases are referred to as activation, adaptation and degeneration, and CR and GR may participate differentially in each [137].

Activation refers to those effects which occur cyclically as a result of variations in circulating glucocorticoids during the diurnal cycle; and it is expected that CR would be heavily involved because it is sensitive to low levels of corticosterone. Activational effects include increased appetite and exploratory activity at the beginning of the waking period, as well as increased efficacy of synaptic transmission in the hippocampus during the waking period [137]. The appetite-stimulating effect may be related to the glucocorticoid–noradrenaline interaction in the PVN, described above. Moreover, the synaptic efficacy change may be related to the interactions between glucocorticoids and the noradrenergic system which were also summarized above.

Adaptation refers to effects of glucocorticoids which result from repeated exposure to stress-induced hormone elevations. It would be expected that the GR subtype is heavily involved in adaptational effects, because GR is sensitive to higher levels of corticosterone, such as occur during stress. One example of adaptation, mediated by glucocorticoid elevation, is the reduction in adrenergic sensitivity in cerebral cortex that results from repeated stress (see above). In contrast, repeated stress elevates central serotonin sensitivity measured by stereotyped behavior elicited by a serotonin agonist, 5-methoxy-*N*,*N*-dimethyltryptamine [38], and glucocorticoids act to *oppose* this increase [37, 39]. In other words, glucocorticoid actions in adaptation mediate some of the effects of stress and oppose others. The brain changes as a result of the process of adaptation to repeated stress, and the net result is the sum of those changes produced by the neural aspects of stress plus those changes produced by glucocorticoid elevations.

The third aspect of glucocorticoid actions in brain is neural damage, and adrenocortical secretions potentiate neural damage and neuronal loss elicited by excitotoxic agents and by hypoxia [138, 139] and appear to do so via the GR receptor subtype [140]. Hypoxia results in increased excitatory amino acids and thus mimics the situation with exogenous excitotoxins; the common denominator, therefore, appears to be need for increased energy metabolism under extreme excitation, and glucocorticoids enter the picture by compromising the ability of the neurons to obtain adequate supplies of metabolizable substrates [141]. Moreover, glucocorticoids are involved in the progressive loss of neurons from the hippocampus which occurs with age in the rat and which can be mimicked in younger animals by prolonged treatment with corticosterone over 12 weeks [140]. Insofar as catecholamines are involved in regulating cerebral blood flow and arrival of glucose, they may be involved in the response to excitotoxins and to hypoxia.

Conclusions

The impact of glucocorticoids on the nervous system is far-reaching and complex, involving neural development, mature functioning of neurons, and the process of aging, as well as the response to hypoxia, as in stroke. Moreover, the balance between normal and aberrant cognition and affect is influenced by glucocorticoids. That is, when we travel, our "jet lag" reflects the fact that our adrenal steroid rhythm lags behind other rhythms and must be reset and resynchronized. And when we are under stress, our ability to cope is influenced by the output of glucocorticoids and their adaptational effects on the brain. In these two types of processes, we have seen evidence in this review for participation of

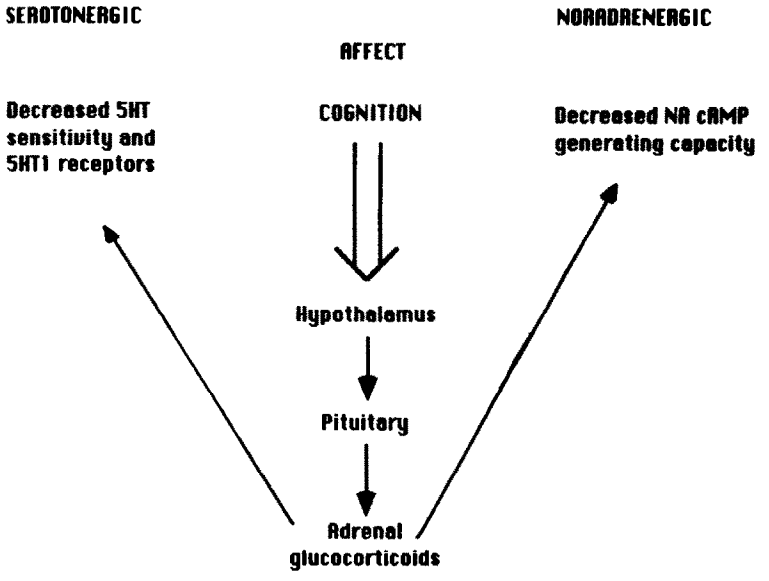

Fig. 3. Monoamines, glucocorticoids, neurochemistry and behavior. The serotonergic and noradrenergic systems of the brain are important for the affective state as well as for cognitive processes, and they are influenced by stress. Glucocorticoids mediate some of the effects of stress on these two systems by decreasing sensitivity at the receptor level and at the level of second messenger generation. In the case of the serotonergic system, glucocorticoids oppose the neural effects of stress to increase central 5-HT sensitivity. This may also happen in the case of noradrenaline sensitivity.

biogenic amine neurotransmitters, and we see multiple points in their biochemistry at which glucocorticoids exert influences. In particular, glucocorticoids decrease sensitivity to serotonin in the CNS, and this is manifested, at least in part, by discretely localized decreases in serotonin-1 receptors. Repeated stress and repeated treatment with glucocorticoids also suppress the cyclic AMP response to noradrenaline (Fig. 3). What is not clear is how these decreases in sensitivity come about. Such decreases might happen through genomic actions of the steroid to induce an inhibitor or to decrease synthesis of critical components of the serotonin receptor and the noradrenaline-stimulated cAMP response system. Alternatively, the decreases might arise through down-regulation and desensitization evoked by stress and adrenal steroid-induced release of serotonin and noradrenaline respectively. Consistent with the second possibility, as far as serotonin is concerned, is that glucocorticoids potentiate serotonin turnover evoked by stress; what is not clear is whether glucocorticoids also potentiate increases in noradrenaline turnover evoked by stress. Further research is required to pinpoint the steps where glucocorticoids influence biogenic amine synthesis, release and receptor mechanisms.

One of the challenges for future research is to understand better the underlying mechanisms by which glucocorticoids exert their influences upon biogenic amines. The local membrane actions of steroids are coming under increasing scrutiny, at the same time as we are gaining increased insight into the genomically-mediated actions of glucocorticoids in neural tissue. Receptors for membrane actions have been detected by binding assays, but they are difficult to study routinely [142]. The receptors for genomic actions have been now recognized as having two subtypes, which respond to different levels of circulating hormone (Fig. 2). These subtypes differ in regional distribution within the brain, leading to the likelihood that diurnal variations of glucocorticoid levels and stress-induced secretion each activate different patterns of brain cells, leading to regionally-different as well as neurochemically-different responses. Each response and each brain region must be dealt with separately in order to understand its relevance to activational, adaptational or degenerative processes with which it is found to change.

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