RESEARCH PAPERS

Steroid Effects on Brain Functions: An Example of the Action of Glucocorticoids on Central Dopaminergic and Neurotensinergic Systems

William Rostène[1], Alain Sarrieau[1], Arnaud Nicot[1], Valérie Scarceriaux[1], Catalina Betancur[1], Danielle Gully[2], Michael Meaney[3], Wayne Rowe[3], Ronald De Kloet[4], Didier Pelaprat[1], Anne Berod[1]

[1]Inserm U. 339, Hôpital St-Antoine, Paris, France

[2]Sanofi Recherche, Toulouse, Cedex, France

[3]Lab Developmental Neuroendocrinology, Centre de Recherche, Hôpital Douglas, Montreal, Quebec, Canada

[4]Sylvius Labs, Bio-Pharmaceutical Science Centre, University of Leiden, Leiden, The Netherlands

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It is now clearly established that steroid hormones released from peripheral endocrine glands may, through specific receptors in the brain, directly regulate brain function. These effects may be rapid or involve long-term modifications at the genomic level. Concerning the glucocorticoids, their receptors are found in most neuronal cells, an observation which can be related to their widespread effects on neuronal metabolism. Furthermore, glucocorticoids are often related to stress. We have previously demonstrated that neonatal handling of the rat prevented excessive endocrine response to stress. In adults, this action appeared to protect the animal from potential damaging effects of glucocorticoids and from related impairment of cognitive functions. The effects of glucocorticoids are thought to involve an interaction of several central neurotransmitter systems. One such neurotransmitter is neurotensin, a neuropeptide which was reported to be closely related to central dopaminergic system regulation. This paper presents a rapid overview of the central effects of glucocorticoids and possible evidence for the interrelationship between these steroids, dopamine and neurotensin systems in the regulation of the hypothalamo-pituitary-adrenal axis. It provides a new way to approach stress responses and to develop new substances that may become potential drugs in the treatment of some psychiatric disorders.

Key Words: glucocorticoid receptors and stress, neuronal cell death, handling paradigm, dopamine, neurotensin, neurotensin receptor antagonist

INTRODUCTION

Glucocorticoids (GCs) synthetized and released from the adrenal glands have a variety of functions in the body, and many of these allow the organism to mount an adequate stress response to physiological insult (Munck and others 1984; McEwen and others 1986). Indeed, the activation of the hypothalamo-pituitary-adrenal axis (HPA) is a basic mechanism of survival in mammals. During stress, the increased secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary induces the release of GCs from the adrenal cortex. GCs, through specific receptors located on peripheral target organs, produce such metabolic changes

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Address reprint requests to: Dr William Rostène, Inserm U. 339, Hôpital St-Antoine, 184, rue du Faubourg St-Antoine, 75012 Paris, France.

as lipolysis, glycogenolysis, maintenance of elevated blood glucose in order to provide an increased availability of energy substrates for the behavioral responses to stress and environmental challenges. These effects, most of which are beneficial in the short term, may lead to serious problems if GC levels remain elevated over a prolonged period of time as shown in steroid-induced diabetes, immunosuppression, infection, and in some mental disorders (Bindley and Rolland 1989; Pearson-Murphy 1991). Therefore, once the stress period is over, it is in the body's best interest to "turn off" the GC response in order to maintain homeostasis.

The efficacy of this process is determined by the ability of GCs to block subsequent ACTH release through an inhibitory feedback action. This feedback is dependent on specific GC receptors located in the pituitary gland, in the hypothalamus, and in various extrahypothalamic regions of the brain. The most notable of these regions is the hippocampus, which has been clearly shown to contain a high amount of GC receptors and to exert an inhibitory influence over the HPA activity (McEwen and others 1986).

Corticosteroid receptors in the brain

It is now well established that 2 types of corticoid receptors are present in the brain. The mineralocorticoid receptor (MR) is largely restricted to the septo-hippocampal system. It binds both corticosterone (CS) and the mineralocorticoid aldosterone with high affinity in the rat, and binds the synthetic glucocorticoid agonist RU 28362 with a lower affinity. The glucocorticoid receptor (GR) has a widespread distribution throughout the brain, binds CS, dexamethasone and RU 28362 with high affinity, and aldosterone with low affinity. Although both receptors bind CS, the affinity of the MR for CS is higher (0.5 nM to 1.0 nM) than that of GR (2.0 nM to 5.0 nM) (Reul and De Kloet 1985). These receptors have been distinguished on the basis of the sequences and neural distribution of their cDNA (Evans and Arriza 1989). Several findings based on the occupation of both receptor types during stress and nonstress conditions strongly suggest that GR is responsible for the negative-feedback actions of the glucocorticoids under poststress conditions (Rotsztejn and others 1975; Reul and De Kloet 1985; Meaney and others 1988). Similar biochemical considerations can be drawn from works carried out in the human brain. Tritiated [^{3}H] cortisol was unable to bind to brain receptors due, in part, to the occupation of the binding sites by endogenous cortisol (Sarrieau and others 1989). This problem was overcome by using the high-affinity GR agonist ^{3}H-RU 28362 or the GR antagonist ^{3}H-RU 38486 (Sarrieau and others 1988). By means of in vitro receptor autoradiography, we demonstrated the presence of GR in the human brain (Sarrieau and others 1986). Autoradiograms showed a dense labeling not only in the hippocampus but also in the human entorhinal cortex, the amygdaloid complex, olivary nucleus, the hypothalamus, the caudate putamen, and the substantia nigra (Sarrieau and others 1986; Sarrieau and others 1989). Interestingly, by means of the antagonist ^{3}H-RU 38486 and several unlabeled competitors, we were able to distinguish clearly between the binding of RU 38486 to GR in the hippocampus, and the binding of this compound to preferential progesterone receptors in the cortex (Sarrieau and others 1986). It is an important observation with respect to the impact of these hormones as modulators of cognitive functions and affective states in humans.

Glucocorticoids and cognitive deficits in aging

GCs serve to protect the organism during stress by coordinating several essential central and peripheral functions. Chronically elevated levels of GCs on the other hand may be the cause of cognitive deficits primarily observed in the aging brain. Long-term exposure to high levels of GCs in the rat induces immunodeficiency, may potentiate neuronal dysfunction, and may result in selective neuronal loss. Hippocampal neuron loss has been associated with aging in rats, and it has been shown that neuronal loss was positively correlated with the increase in HPA activity (Landfield and others 1981). Several lines of evidence suggest that GCs are indirectly responsible for the loss of hippocampal neurons increasing the neuronal electrical and metabolic vulnerability. This hypothesis is based on a series of experiments conducted by Sapolsky's group (Sapolsky 1990) which showed that GCs inhibited glucose uptake by hippocampal neurons and glial cells (Horner and others 1990), potentiated the effects of excitotoxins, and inhibited glutamate uptake by glial cells (Virgin and others 1991), a major route for the elimination of this excitatory aminoacid from the synapse. These findings suggest that GCs may compromise hippocampal neuronal survival by enhancing the availability of glutamate associated with a range of neurological insults. This is supported by the fact that NMDA receptor antagonists block the neuronal loss induced by GCs (Armanini and others 1990). Only neurons from the CA1 region and the apical dendrites of the hippocampal CA3 subfield are sensitive to GCs, possibly accounting for regional selectivity of the effect of GCs (Sapolsky 1990; Gould and others 1990). Similarly, GCs were shown to block the postsynaptic excitatory electrophysiological signals in the hippocampus (Joels and De Kloet 1994), suggesting another possible mechanism for changes in cognitive functions in response to GCs. Such GC action can be put in the context of homeostasis. Electrophysiological data in the rat showed that MR is important for the stability of neurotransmission in hippocampus, i.e., excitatory (glutamate, noradrenergic systems), whereas inhibitory actions (serotonin) of neurotransmitters and ion regulation such as calcium are minimal under low MR occupancy (low

plasma corticosterone). Absence of GCs and excess GCs both give similar enhanced responses in order to restore homeostasis in extreme situations (Joels and De Kloet 1994). It is easy to understand that disruption of this homeostasis by long-term exposure to GCs may lead to irreversible disturbances such as cognitive deficits. Since the most prominent features of the hippocampus stem from its capacity to direct attention to behaviorally relevant stimuli, to provide a base of working memory, and to allow behavior modification in the face of changing cues and probabilities of success (McEwen and others 1987), hippocampal neuronal loss or changes in the neuronal electrical properties induced by GCs may dramatically influence these behaviors.

Although human aging does not appear to alter resting cortisol and ACTH plasma levels substantially, a growing body of evidence suggests an enhanced HPA axis responsiveness with aging. The hippocampal neurotoxicity of GCs reported in the rat, the hippocampal impairment of cognitive function in patients with Cushings' syndrome or after GC administration in normal volunteers (Wolkowitz 1994) support the possibility that enhanced HPA axis activity contributes to central events underlying cognitive impairments in late life.

Neonatal handling of the rat as a model of long-term adaptation to stress

Based on animal studies, it was recently suggested that individual changes in the HPA activity in late life may be dependent upon our own experience of stress during life. Evidence shows that individuals respond differently to the same stressor and are more or less able to cope with stress. A postnatal handling procedure consisting of removing rat pups from their cages, placing the animals together in small containers, and, 15 minutes later, returning the animals to their cages and their mothers, has been a very fruitful animal model in showing how early experiences produce adaptation responses that are seen in adulthood.

We have used this handling paradigm extensively to examine how subtle variations in the early environment may alter the development of specific neurochemical systems, leading to individual differences in response to biological stimuli that threaten homeostasis (Meaney and others 1991). Thus, handling increases GC receptor densities in the hippocampus, effectively enhancing the efficacy of the feedback inhibition of GCs on ACTH release. These effects are reflected in the differential secretory pattern of CS in handled and nonhandled animals following stress (see Figure 1).

Handling also increases hippocampal serotoninergic (5-HT) turnover (Meaney and others 1994), with parallel increases in hippocampal GC receptors (Mitchell and others 1990); effects which persist well beyond the period of the treatment. Since the handled animals present a better response to stress in adulthood than nonhandled rats (Meaney and others 1991, 1994) (see Figure 1), the data on 5-HT systems may represent a neurochemical basis for the possible association of high cortisol levels with endogenous depression (major affective disorder) in humans (Pearson-Murphy 1991).

In addition to these effects, GCs also regulate neurotransmission in a number of brain regions through their effects on transmitter turnover, receptor biosynthesis, and postreceptor effector systems throughout life (McEwen and others 1986). It is not the aim in the present review to discuss all the interactions between GCs and neurotransmitters, the latter being either classical neurotransmitters (acetylcholine, amines, excitatory aminoacids) or neuropeptides. We will only briefly focus on one aspect of the effects of GCs not covered in review papers: the interaction of GCs with central dopaminergic (DA) and neurotensinergic (NT) systems.

Interaction of GCs with central dopaminergic and neurotensinergic systems

There is general agreement that central catecholamines play a pivotal role in the neural regulation of ACTH release and behavioral adaptation, particularly during stress (Ganong 1980). Catecholamines are generally believed to exert a stimulatory role on HPA activity through the ventral noradrenergic ascending bundle originating in the lower medulla and projecting to the paraventricular nucleus of the hypothalamus (Plotsky 1991; Gaillet and others 1993). Not only are adrenergic pathways thought to play a role in the regulation of the HPA axis, but central DAergic systems may also be involved. It was recently reported that isolation stress increases tyrosine-hydroxylase mRNA (the rate-limiting enzyme of DA synthesis) in the ventral tegmentum and substantia nigra, 2 structures of the midbrain from where the ascendant mesolimbic cortical and nigro-striatal pathways originated (Angulo and others 1991). These pathways are known to be involved in motivation and motor activity.

Casolini and others (1993) also reported that selective lesions of the mesencephalic DA neurons decreased basal and stress-induced corticosterone secretion in the rat. Interestingly, DA neurons are the prime target for antipsychotics (Le Moal and Simon 1991). This neuronal system is also thought to play a key role in addiction since addictive drugs have been found to activate mesencephalic DA systems (Le Moal and Simon 1991). In addition, it has been shown that activation of DA neurons with amphetamines (Knych and Eisenberg 1979) or cocaine (Borowsky and Kuhn 1991) enhanced plasma CS levels. In contrast, injection of GCs increased central DA activity while CS depletion by adrenalectomy reduced it (Rothschild and others 1985; Versteeg and others 1983). This finding suggests a link between the central DA system and the HPA axis, and this interaction may be

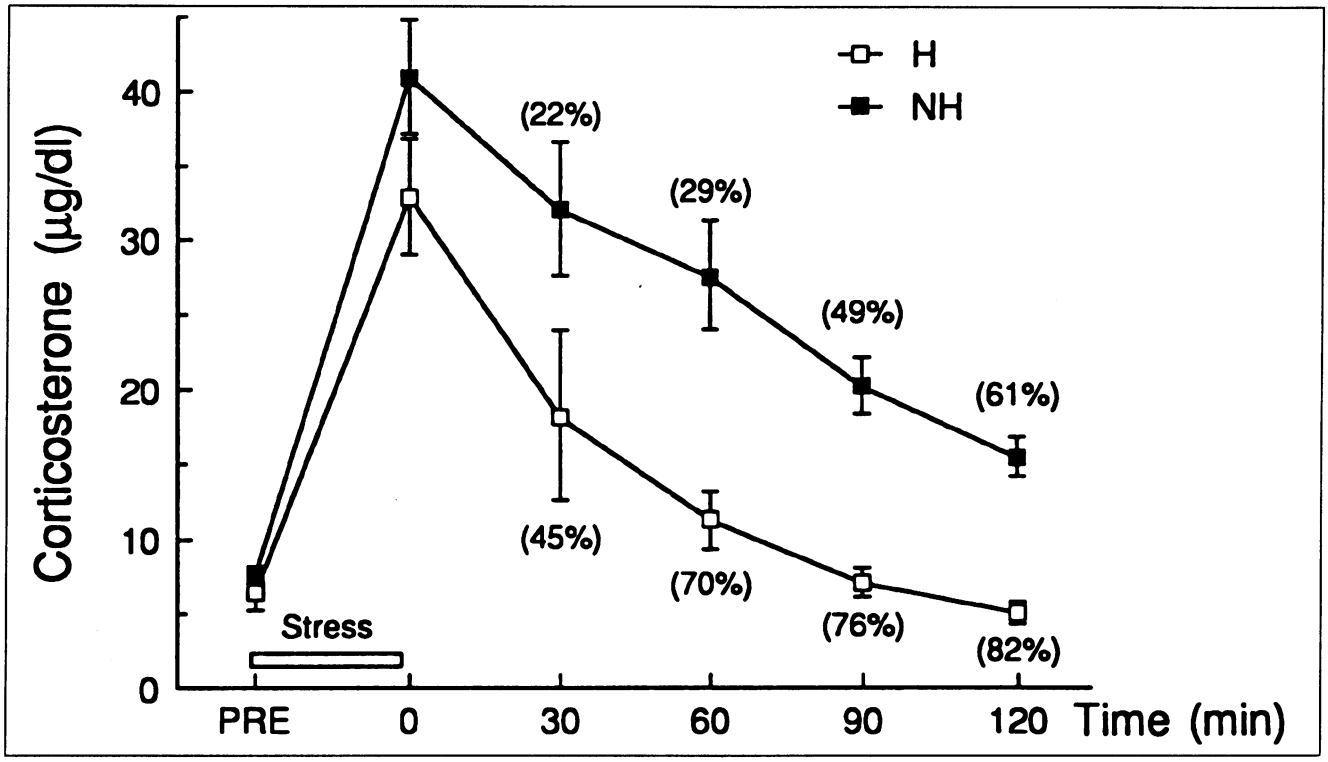

Figure 1. Time course of corticosterone secretion prior to, during and following 20-min restraint stress in adult-handled (H) and nonhandled (NH) rats. The time points refer to the number of minutes poststress, with the 0 time point representing the peak stress value. The group differences are significant ($p < 0.05$) for all time points after stress. The values in brackets represent the percentage decline from the peak stress value (100%) for each group. The decrease in CS levels after stress is faster in the H rats than in the NH rats. (Meaney and others 1991).

involved in certain psychopathological conditions such as depression, addiction and schizophrenia (Swerdlow and Koob 1987).

There is a great deal of evidence based on neurochemical, behavioral and, more recently, anatomical data suggesting an interaction between central neurotensin (NT) and central DA systems (Rostène et al 1992). These studies have focussed mainly on the nigrostriatal and mesolimbic DA pathways. The first evidence is probably related to the physiological effects observed after administration of NT in the nucleus accumbens resulting in inhibition of the hyperlocomotion induced by DA agonists. However, NT has been also shown to produce increases in DA turnover and release in several brain regions rich in both DA terminals and DA cell bodies and dendrites. In contrast, a reciprocal interaction between NT and DA has also been described. Changes in NT concentrations in the basal ganglia following either neuroleptic treatment or lesioning of the central DA systems have been reported (Kitabgi and Nemeroff 1992). The neurochemical and behavioral changes induced by NT have prompted several authors to postulate that NT could act as a neuroleptic-like substance. Though such a hypothesis based on the blockade, like neuroleptics, of the locomotor activity induced by DA agonists, is not as clear now as when it was first suggested, it allowed a great deal of studies on the subject (Kitabgi and Nemeroff 1992).

The physiological effects following central administration of NT are likely to be mediated by specific binding sites for the peptide. Specific high affinity NT binding sites have been described in both the substantia nigra and the ventral tegmental area. These 2 mesencephalic regions are known to contain high densities of DA perikarya. Similarly, the striatum, nucleus accumbens and prefrontal cortex, major projection sites of those DA pathways, also express high amounts of NT binding sites both in animal and human brains (Rostène and 1992).

Like DA, central administration of NT has been shown to be involved in the regulation of HPA activity. When administered intracerebroventricularly, NT increased plasma levels of ACTH (Fuxe and others 1984) and CS (Gudelsky and others 1989). Rowe and others (1995) showed that the NT-induced activation of the HPA axis might be mediated by an enhanced release of corticotropin-releasing hormone (CRH) from the median eminence to the portal vessels, since

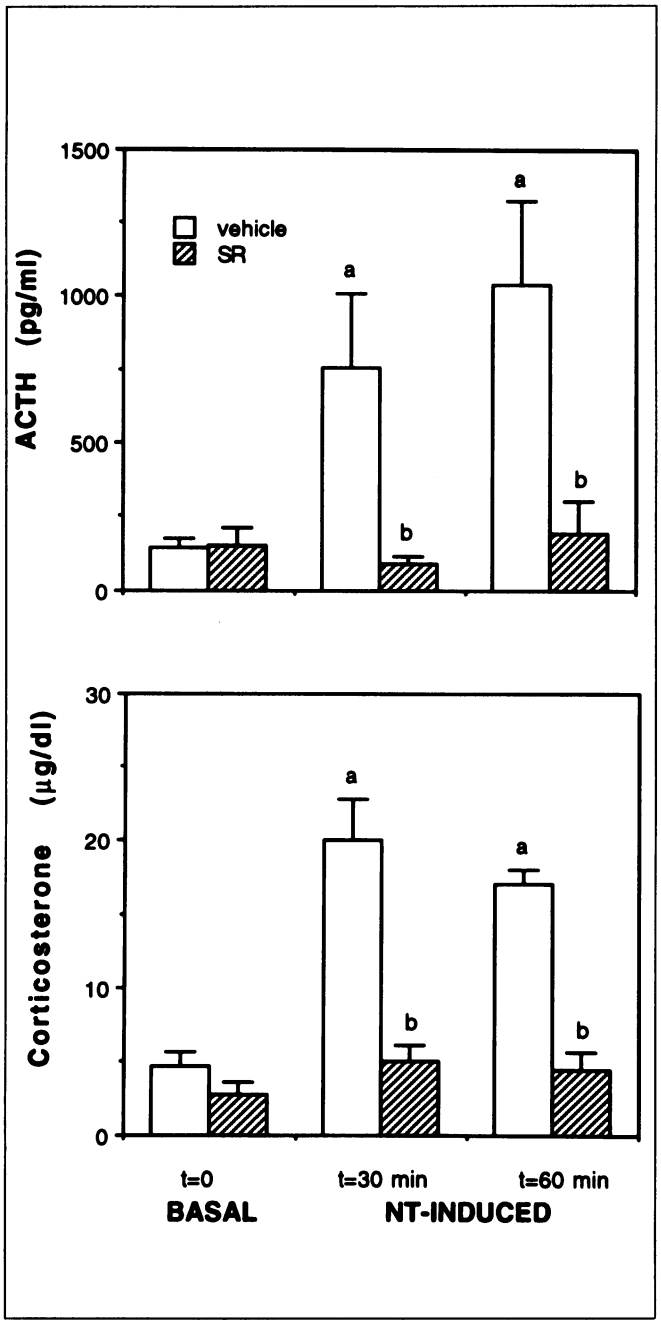

Figure 2. Effects of icv injection of either 10 nmol SR 48450 (striped bars) or vehicle (white bars) on basal and NT-induced plasma ACTH and corticosterone levels. Time indicates the delay after the icv NT (0.6 nmol) injection. SR 48450 or its vehicle were icv injected 1 hour before NT. Values are means ± SEM (n = 5-8 for each group) and statistical analysis was carried out using the Student's *t*-test (a: different from basal values; b: different from NT injected group pretreated with SR vehicle; statistical significance $p < 0.02$ for ACTH values and $p < 0.01$ for corticosterone values). (Nicot 1994).

pretreatment of the animals with the CRH antagonist α-helical CRH attenuated this effect. Direct neuroanatomical connections between NT and CRH neurons may underline the stimulatory effects of NT since NT immunoreactive nerve fibers and NT binding sites have been observed in the parvocellular part of the paraventricular nucleus of the hypothalamus (Moga and Saper 1994; Nicot and others 1994) where CRH-producing neurons are located.

However, until recently, the physiological relevance of such data was hampered by the lack of selective NT antagonists that could specifically block the NT effects at the level of their interaction with specific receptors. For that purpose, we recently developed new potent and selective nonpeptide NT receptor antagonists such as SR 48692 (Gully and others 1993) with SANOFI, which have the capacity to bind with a nM affinity to NT receptors and to cross the blood-brain barrier.

As shown in Figure 2, intracerebroventricular injection of 0.6 nmol of NT induced a 4- to 5-fold increase in circulating ACTH levels 30 and 60 minutes postadministration. The same pattern was observed with plasma CS levels. Whereas no significant change was obtained 1 hour after intracerebroventricular injection of SR 48450, an analog of SR 48692, in the basal levels of circulating ACTH and CS, pretreatment of the animals with 10 nmol of SR 48450 completely blocked the NT-induced HPA activation at 30 or 60 minutes after the NT injection. Recent data from our group show that SR 48692 also attenuated ACTH and CS release following restraint stress (Rowe and others 1993). Further, the afternoon rise in ACTH and CS was also reduced following chronic SR 48692 exposure to paraventricular neurons, suggesting an endogenous role for NT in stimulated HPA activity.

In contrast, GCs themselves may influence the central activity of NT. Mild electrical footshock stress in the rat increased NT concentrations in the discrete DA cell body groups of the lateral ventral tegmental area (Kilts and others 1992). Moreover, ether or immobilization stress was shown to increase NTmRNA in the paraventricular nucleus in the rat (Watts 1991; Ceccatelli and Orazzo 1993). Interestingly, as shown in Figure 3, we observed that GCs can increase the intracellular content of NT in rat hypothalamic cells in culture, an effect mediated by type II GC receptors, since RU28362 and dexamethasone gave similar results (Scarcériaux and others 1995). All these data support the possible role of endogenous NT in regulating HPA activity.

In spite of rather straightforward relationships such as the link between adrenal steroid hypersecretion and endogenous depressive illness, and the use of the dexamethasone suppression test to diagnose this disorder (Pearson-Murphy 1991), the connection between GCs and mood is not completely understood. In the context of homeostasis, the critical issue is where the beneficial function of GR ends and the damaging effect starts. GC excess promotes traits recognized in

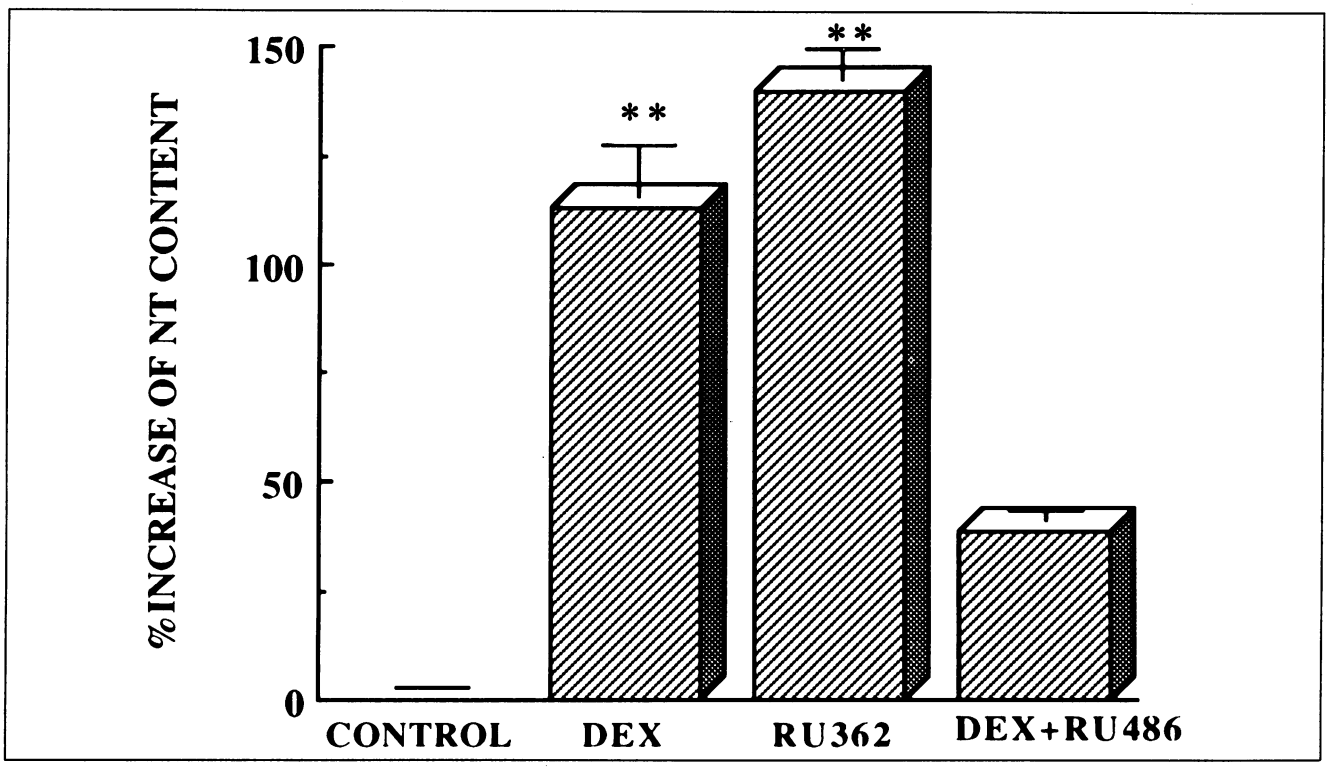

Figure 3. Effect of glucocorticoids on intracellular neurotensin (NT) content from rat hypothalamic cells in primary cultures. After a 48-hour treatment with the various steroids (1 μM), intracellular NT levels were measured by radio-immunoassay following extraction with 0.1 N HCl. Values represent the mean ± SEM of the percent increase NT versus control (4 experiments). Statistical analysis was performed with Dunnett's *t*-test; ** $p < 0.01$. (Scarcériaux and others 1995).

depressive illness such as anxiety, agitation, dysphonia, sleeplessness, and psychotic episodes. What is puzzling is why the absence of GC can lead to some of the same symptoms. The difference can be based on adaptation processes related to the duration of exposure and not to GCs themselves (McEwen and others 1987). In physiological conditions, GCs decrease excitatory neurotransmission and, in response to stress for instance, can restore excitability (homeostasis) of the neuronal cell transiently raised by excitatory stimuli (Joels and De Kloet 1993). As illustrated in this paper, long-time exposure to GCs can affect this homeostasis through an action on various central neuropeptides and neurotransmitter pathways, thus influencing the neurochemistry and functioning of several brain functions. For instance, as shown for the central NT systems, it is easy to imagine how different the psychological effects of GCs will be if they either modulate the central dopaminomimetic or the neuroleptic-like action of NT, depending on their site of action.

Our knowledge of the complex mechanisms underlying depressive illness, degenerative diseases, as well as normal response to stressful stimuli and experiences may allow us to examine new types of drugs which may become, in the near future, potent new tools to study and treat psychiatric disorders.

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