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Full-length review

The acute effects of corticosteroids on cognition: integration of animal and human model studies

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Abstract

Cognitive deficits following acute administration of corticosteroids have been described in experimental animals and humans. In both populations, an inverted-U shape relationship has been reported between the dose of corticosteroids administered and the nature and extent of the cognitive deficits induced by corticosteroids. Further studies in animals have revealed a two-level recognition system for adrenal steroids, which was later more clearly resolved into two receptor types: Type I and Type II adrenal steroid receptors. The demonstration of an inverted-U shape relationship between corticosteroids and cognitive process leads to the question as to whether this relationship is generated via the two receptor types, exerting effects either via competing or opposing processes or via a more synergistic interaction. In this article, we review the effects of corticosteroids on animal and human cognition and propose a theoretical framework that leads to testable predictions regarding the acute effects of corticosteroids on cognitive function. We also discuss some methodological and experimental factors that might explain some discrepancies in data obtained from animals and humans. Furthermore, we suggest new experimental protocols for use in humans, based on animal literature, that could help resolve these discrepancies and assess more clearly the nature of the cognitive deficits induced by acute administration of corticosteroids.

Keywords: Corticosteroid; Cognition; Receptor; Animal; Human

Contents

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1. Introduction

Steroid hormones of the adrenal cortex regulate energy storage and mobilization and help to maintain electrolyte balance, and they also have important effects in the brain, altering excitability of nerve cells throughout the diurnal cycle and in the aftermath of stressful experiences by modifying neurochemical and structural features of the brain. Early clinical investigations revealed effects of glucocorticoid deficiency in decreasing the integration of sensory information, while more recent clinical observations have pointed to pathophysiological effects on the brain of elevated endogenous glucocorticoid levels, namely, in treatment-resistant depressive illness and in tests of cognitive function. In fact, it is the recent resurgence of interest in the studies of the acute and chronic effects of adrenal steroids on human cognitive function and affective state that have catalyzed attempts to integrate what is known from animals studies with the growing human clinical literature on this topic.

The task of doing so is a huge one, because the studies on humans and animals encompass both the acute actions of adrenals steroids, the chronic effects of adrenal steroid administration or stress, as well as the aging process. A recent book by Sapolsky [169] has reviewed the role of adrenal steroids in long-term degenerative changes, and the topic of aging from a developmental perspective has been treated in several current reviews [109,121]. What is missing is an account of the more acute actions of adrenal steroids and a discussion of the important differences in access to target tissues between synthetic and natural adrenal steroids, since a great deal of knowledge about glucocorticoid actions in humans and in animals is based upon the effects of synthetic steroids such as dexamethasone. Acute effects of adrenal steroids must be considered from the standpoint of their actions on neuronal excitability [85–87]. One cannot consider this topic without also discussing adrenal steroid receptor types and their distributions, as well as the role of corticosteroid binding globulin (CBG) and steroid metabolizing enzymes in limiting the access of natural adrenal steroids to their receptors. The aim of this review is to summarize data on the effects of corticosteroids in the domains of animal and human cognition by taking into account these endocrine variables. Whereas the first part summarizes the empirical studies performed in both domains, the second part of the review is devoted to an attempt at integrating these data and to offer a speculative model of the general effects of corticosteroids on animal and human cognition.

2. Historical background

In 1855, Thomas Addison described for the first time what he then called a 'dark skin disease' [1], a pigmentary characteristic that he found to be associated with pathological modifications of the adrenal glands. One year later, Brown-Séquard [32] showed the importance, for an animal's life, of these 'small capsules' and confirmed Addison's observations. From these two pioneer works, a large number of studies have recognized the function of the adrenal cortex in glucose metabolism through synthesis and secretion of specific hormones, particularly corticosteroids [35]. A century after Addison's observation occurred what some authors have named the "most cataclysmic event in the history of corticosteroid endocrinology" [134], that is, the discovery, by Hench and collaborators [75], of the therapeutic effects of corticosteroids on inflammatory diseases such as rheumatoid arthritis and asthma. However, the enthusiasm engendered by these preliminary observations was dampened few years later by the finding that the therapeutic use of corticosteroids is followed by several side effects, particularly on affect and cognition [39,199]. These include symptoms such as emotional lability, anxiety, distractibility, pressured speech, sensory floding, insomnia, depression, and cognitive impairment. The nature and magnitude of these disturbances has led researchers to categorize these symptoms under the term 'steroid psychosis' [39].

The origin of such effects is still unknown. However, many have postulated that, whatever may be the origin of

such symptoms, the excessive concentrations of the steroid may access the brain and exacerbate, perpetuate or modify the presentation of mental symptoms associated with corticosteroid administration. Such a hypothesis was appropriate since in 1943, Harris had completed a series of landmark anatomical studies that clearly established that the central nervous system regulates the HPA axis [73]. Starting in 1968, McEwen and collaborators reported that the hypophysiotropic area was not the only target for steroid action, and they described the presence of adrenal steroid receptors in extrahypothalamic limbic brain regions of the rat [115,116]. In these studies, uptake and retention of adrenal steroids by brain tissue indicated the presence of receptors, and the highest amount of accumulation occurred in the hippocampus. Subsequently, cytosol receptors and cell nuclear receptors were characterized [71,72,117], and radioimmunoassay was used later to detect endogenous steroids retained by cell nuclei and thus provide validation for the istotope uptake [118]. Along with discrepancies in uptake of ^{3}H dexamethasone and ^{3}H corticosterone (for a review, see [120]), these studies revealed a two-level recognition system for adrenal steroids [52], which was later more clearly resolved into two receptor types, Type I and Type II receptors [153].

3. Corticosteroid receptor types

3.1. Receptors actions

Corticosteroid hormones act via intracellular receptors that mediate slow genomic actions. The binding of the corticosteroid hormone to its receptor induces a conformational change in the receptor, and leads to dissociation of the receptor from its attached protein [8]. The activation of specific nuclear translocation signals induces a dimerization of the receptor complex and the receptor dimer binds to the hormone responsive element of the nuclear DNA, at which point transcription is initiated. As a consequence, translation of mRNAs to certain proteins is affected and may eventually result in steroid-induced alterations.

Although the slow genomic actions of corticosteroids are well-described, many studies performed over the past decades reported the occurrence of rapid steroid effects. In this case, membrane rather than intracellular steroid receptors seem to be implicated. During uptake into the cell, it is postulated that corticosteroids are metabolized and interact with membrane-associated receptor proteins. This process may lead to modulation of membrane characteristics [82], or transmitter response ([111]; for a review, see [172]), and give rise to the rapid actions of corticosteroids.

3.2. Receptor types and distribution in the brain

Both Type I and Type II corticosteroid receptors have been cloned and shown to be the product of different genes, although they share some homology in the DNA binding domain [3,81,126]. Agonist compounds elicit glucocorticoid responses and their activity depends on their affinity for the receptors and on their plasma concentrations. Type I receptors in animals and humans have a high affinity for corticosterone and aldosterone, while Type II receptors have a somewhat lower affinity for aldosterone (for a review, see [119]), as well as a high affinity for dexamethasone, a synthetic corticosteroid (see [119]).

Other steroids bind to the steroid receptors but do not elicit glucocorticoid responses. These antagonists compounds compete with agonists for binding to the receptors and therefore, block the agonist response. Numerous analogues of corticosterone and aldosterone, as well as Type I and Type II receptor antagonists have now been synthetized and show high specificity for the receptors. Table 1 presents the most widely used of these compounds.

Table 1
Characteristics of Type I and Type II corticosteroid receptors (the specific references for each of these characteristics are given in text)

	Type I	Type II
General:	resembles the kidney mineralocorticoid receptor	resembles the liver glucocorticoid receptor
	two functional expressions in the brain:	one functional preferring site:
	mineralocorticoid receptor	glucocorticoid receptor
	corticosteroid preferring site	
Distribution:	limbic system	limbic system
	brainstem motor nuclei	brainstem monoaminergic nuclei
		paraventricular nucleus
		hypothalamic nuclei
		cerebral cortex
Agonist (affinity):	dexamethasone (+)	dexamethasone (+ + +)
	corticosterone, cortisol (+ + +)	corticosterone, cortisol (+ + +)
	aldosterone (+ + +)	aldosterone (+)
Antagonist (affinity):	spironolactone (+ +)	RU38486 (+ + +)
	RU26752 (+ + +)	
	RU28318 (+ + +)	
High-dose Type I agonist:	down-regulation	down-regulation
High-dose Type II agonist:	increased availability	down-regulation

In the brain, Type I receptors are more heterogeneously expressed than Type II receptors, with highest levels of expression in the limbic system (see below), and certain brainstem motor nuclei. Type II receptors are widely expressed in most brain regions and are detected, among other brain regions, in the paraventricular nucleus and other hypothalamic nuclei, the limbic system, the cerebral cortex, and most brainstem monoaminergic nuclei (see [153] for a review).

3.3. Receptor regulation in the brain

Like many other hormones, the binding of corticosteroids to their specific receptors in the brain depends on the level of circulating steroids. After the removal of the adrenal glands (adrenalectomy: ADX), when there are no corticosteroids in circulation, the binding of labelled corticosteroids rises [153]. At low, replacement levels of corticosteroids, there is an increase in the number as well as the affinity of corticosteroid receptors (up-regulation). The inverse phenomenon arises at high level of circulating corticosteroids, with a decrease in the number and affinity of the receptors (down-regulation).

Type I and Type II receptors are differentially regulated by endogenous and exogenous corticosteroids and this aspect is a common theme of recent papers on the adrenal steroid system in the brain. High levels of synthetic Type II receptor agonists or corticosterone will down regulate Type II receptors, but will increase the capacity of Type I receptors [154,178]. On the contrary, mineralocorticoids will down regulate both receptor types, while Type I receptor antagonist (particularly spironolactone) will have the opposite effect [31,107,177]. Finally, it has been shown that these changes in receptor binding are preceded by transient changes in mRNA levels, which suggests that the adrenal steroids affect the turnover rate of the receptors [155].

3.4. Effects mediated by Type I and Type II receptors

Changes in neurons physiology, morphology and neurogenesis are induced by treatment with Type I and Type II

Table 2
Effects on hippocampus and other brain regions mediated by Type I and Type II receptors

Effect	Brain region	Receptor type	References
Excitability:			
LTP	hippocampus, CA1, DG, CA3		
facilitation	DG, CA1, CA3	Type I	[54,85,144]
inhibition	DG,CA1,CA3	Type II	[54,85,144]
depression (LTD)	so far, only DG	Type II	[145]
Calcium channels	hippocampus, CA1		
facilitation	so far, only CA1	Type II	[90]
inhibition	so far, only CA1	Type I	[87]
Muscarinic response to carbachol	hippocampus, CA1		
inhibition	so far, only CA1	Type I	[78,79]
5-HT_{1A} response	hippocampus, CA1		
inhibition	so far, only CA1	Type I	[95]
Neurotransmission:			
Neuropeptide Y	hippocampus, hilus	Type I	[192]
Dynorphin	hippocampus, DG	Type I	[193]
Kainate receptors	hippocampus, DG	Type I	[193]
Vasopressin V1 receptors	hippocampus	Type I	[102,166]
5-HT_{1A} receptors	hippocampus, DG, CA3	Type I	[95]
5-HT_{2} receptors	cerebral cortex	Type I	[95]
Corticotrophin releasing factor	hypothalamus, PVN	Type II	[2]
Neurokinin A (substance P)	caudate, bed nucleus	Type I and Type II	[151]
Structural plasticity:			
Granule neuron turnover	hippocampus, DG	Type I	[200]
Damage of pyramidal neuron	hippocampus, CA1, CA3	Type II	[141]

Type II receptor occupancy by the agonist RU 28362 given in a minipump at 10 μg/h suppressed almost to zero the CRH mRNA signal in the paraventricular nuclei (PVN), whereas the Type I agonist, aldosterone (ALDO, 10 μg/h) had no effect [2]. In the hippocampus of the same animals, ALDO prevented the up-regulation of 5-HT1A receptors that was produced by ADX, whereas RU 28362 was without any effects [95]. ADX-induced decreases in dynorphin mRNA in granule neurons of the dentate gyrus and in kainate receptors in the stratum lucidum of CA3 (representing the mossy fiber zone of terminals from dentate granule neurons) are reversed by ALDO but not by RU 28362 treatment ([193]. At the same time, Type I receptors in interneurons of the dentate hilus mediate a negative regulation by adrenal steroids of the expression of neuropeptide Y mRNA [192]. Several other reports indicate that the expression of putative vasopressin and oxytocin receptors in hippocampus are regulated positively by adrenal steroids, with evidence in the case of the V1 vasopressin receptors pointing towards Type I receptor mediation [102,166]. Thus, many of the known actions of adrenal steroids in the hippocampus appear to be mediated by Type I receptors, including the blockade of apoptosis caused in the dentate gyrus by ADX that was described above. Exceptions are the Type II mediated inhibition of LTP, noted above, and the involvement of Type II receptors in the excitotoxin-induced damage to hippocampal neurons in culture [141] that was also noted earlier.

agonists. Since the hippocampus contains both types of receptors and is known to be implicated in animal and human memory function, it has been the major structure studied so far with regard to the effects mediated by Type I and Type II receptors. The physiological response of hippocampal neurons to adrenal steroids administration show a diversity of effects, ranging from a biphasic modulation of excitability (reviewed in [87,120]), to the regulation of neurogenesis and programmed cell death in neurons of the dentate gyrus, and atrophy and death of neurons in the Ammon's horn (reviewed in [120]), two sub-structures of the hippocampus that express both types of receptors [184]. The survival of neurons in the dentate gyrus appears to be maintained via low levels of adrenal steroids acting on Type I receptors [200], while the activation of Type II receptors exacerbates the destructive effects of certain neurotransmitters (particularly excitatory amino acids) on hippocampal neuronal survival [168,169]. Specific Type I and Type II agonists given to ADX rats produce strikingly different effects on various aspects of gene expression in the hippocampus, and these differences reveal both regional differentiation within hippocampus as well as surpinsingly different roles for the two receptors in Ammons horn and dentate gyrus gene expression in the hippocampus. These effects are summarized in Table 2 and are compared with actions mediated by Type I and Type II receptors in other brain regions. There are non-overlapping effects mediated by Type I and Type II receptors in the hippocampus. Taken together with effects on hippocampal neuronal excitability summarized in Table 2 and described in the next section, what is surprising about these non-overlapping actions of Type I and Type II receptors on gene products in hippocampus is that they defy the classical model of adrenal steroid receptor action via a common glucocorticoid response element (GRE) [5,6,58], and point to a different and possibly more complex mode of mineralocorticoid and glucocorticoid regulation of gene expression [129].

3.5. Immediate and delayed actions of corticosteroids on the brain

The time-course of the steroid-induced effects demonstrates a great range. First, steroid actions taking place within minutes after exposure to adrenal steroids have been reported. In most cases, corticosteroids have been shown to rapidly depress the firing activity of neurons [38,170]. This fast onset of the response seems to preclude a genomic mechanism of action and to involve membrane receptors. Second, steroid actions taking place hours after exposure have also been reported and this finding is compatible with a genomic mechanism of action. For example, Pfaff and collaborators [148], studying more delayed actions of corticosteroids, showed that the firing rate of hippocampal neurons is suppressed by corticosterone with a delay of at least 30 min.

Adrenal steroids modulate the ability of hippocampal neurons to show long-term potentiation, or LTP [19]. A single burst of high frequency stimulation to hippocampal afferents immediately alters the responsiveness of neurons to subsequent acute stimulation, an effect lasting over many hours to days. A number of recent studies have demonstrated in the hippocampal CA1 field and the dentate gyrus of the hippocampus that acute stress and acute glucocorticoid elevation produces an impairment of LTP or its close relative, primed-burst potentiation, or PBP [54,55,77]. Subsequently, it was shown that, in both the dentate gyrus and CA1 and CA3 fields, LTP can be modulated rapidly (within 1 h), and biphasically by adrenal steroids acting, respectively, via Type I and Type II receptors ([145,146]; also see Section 4.1). Moreover, in awake, freely moving adrenalectomized rats, the enhancement of LTP by the Type I receptor agonist aldosterone lasts for at least 24 h, at which time it is still markedly higher than ADX rats given only vehicle treatment before LTP induction [147].

How do these biphasic actions come about? Judging from studies on pyramidal neurons of the CA1 region, which must in the future be extended to other hippocampal neuron types, adrenal steroids have been shown to act via Type I and Type II adrenal steroid receptors to maintain and modulate excitability of hippocampal neurons [9,10,17,87]. As summarized in Table 2, Type I receptor activation in hippocampus from adrenalectomized rats is associated with reduced calcium currents through voltage-gated channels, reduced responses to serotonin via 5-HT_{1A} receptors, and to carbachol via muscarinic receptors and stable responses to synaptic inputs involving excitatory and inhibitory amino acids [78,79]. Additional activation of Type II receptors causes increased calcium currents and enhanced responses to excitatory amino acids, serotonin and carbachol [87].

As shown in Table 2, very high levels of Type II receptor activation markedly increases calcium currents [90], and also leads to increased *N*-methyl-D-aspartate (NMDA) receptor expression on hippocampal neurons [194]. Acute stress also increases NMDA R1 mRNA [7]. Kainate receptor mRNA levels are affected by acute corticosterone treatment, with low dose occupancy of Type I receptors increasing mRNA levels for kainate receptor types 1 and 2 [88]. The conclusion from this so-far limited information is that adrenal steroids have diverse effects on the neurochemical systems that affect hippocampal plasticity and underlie adrenal steroid effects on LTP and on learning and memory.

3.6. Receptor distribution: emphasis on brain structures mediating learning and memory

The interaction between the brain structures that express a high level of corticosteroid receptors is of particular importance in determining the effects of corticosteroids on

animal and human cognition. The limbic system contains both types of receptors and is implicated in a number of forms of learning and memory. Although the limbic system has been described in various ways through the years, it is generally defined as a group of interconnected structures in the medial temporal lobe, diencephalon, subcortical gray matter of the forebrain, and septal regions of the frontal lobe. Areas that are often included in the limbic system are the hippocampus, the parahippocampal gyrus, the entorhinal and insular cortices, the amygdala and septal nuclei, the hypothalamus, and anterior thalamus, the nucleus accumbens, the cingulate cortex and the olfactory bulbs.

In general, the limbic structures are thought to subserve the integration of sensory input coming from the environment with affective, cognitive or emotional data. However, lesions to specific regions of the limbic system induce differential effects on learning and memory, leading to a multiple system view of the implication of the limbic system in learning and memory.

It can now be stated with a high level of certainty that the hippocampus is important for memory in humans and non-humans primates (for a review, see [175]). However, recent evidence suggests that the entorhinal, perirhinal and parahippocampal cortex also participate in memory functions. Monkeys with lesions of the hippocampus and surrounding areas are impaired on delayed non-matching to sample tasks while they show a normal performance on certain skill-based or habit-based tasks [131,140,205]. Larger bilateral medial temporal lobe removal induces a level of deficit significantly larger than removal of the hippocampus alone, which suggests that the regions surrounding the hippocampus are also important in learning and memory [206,208].

In 1978, Mishkin [130] reported that monkeys with conjoint but not separate damage to the hippocampus and amygdala are severely impaired in recognition memory for objects. Further quantitative studies of emotional behavior were carried out and showed that either partial or complete damage to the amygdala in monkeys causes detectable changes in emotional behavior as evidenced by an abnormal tendency to approach or touch stimulus objects [209]. In 1991, Zola-Morgan [209] reported a double-dissociation with regard to the cognitive deficits induced by hippocampal and amygdala lesions. Monkeys with amygdala damage exhibit abnormal emotional behavior with memory being unaffected. Monkeys with hippocampal damage exhibit abnormal memory behavior with emotion being unaffected [209]. More recently, a differential contribution of amygdala and hippocampus to cued and contextual fear conditioning was reported [149,150]. In classical cue conditioning, a neutral conditioned stimulus is paired with an aversive stimulus and the capacity of the animal to retain this association is then measured by giving the conditioned stimulus and measuring the conditioned response. By contrast, in context conditioning, an emotional response is elicited by placing the animal in a chamber in which an aversive unconditioned stimulus have previously been experienced. The aversive behavior displayed by the rat when placed in this chamber represents a conditioned response to the context in which the aversive situation has been experienced [18]. These studies, as well as others recently performed in humans [89,203] suggests that the hippocampus and related structures participate in specific kinds of memory functions while the amygdala is important for the acquisition of conditioned fear and the establishment of affective significance for neutral stimuli [48,66,98,99,135].

However, all these cortical substructures in the medial temporal lobe are sites of convergent and reciprocal projections from widespread unimodal and polymodal association areas in the neocortex [4,186]. This has to be kept in mind in the interpretation of the acute effects of corticosteroids on animal and human cognitive process. Since the majority of studies performed in the field of psychoneuroendocrinology in the past three decades were performed using the hippocampal model of learning and memory, we will mainly discuss this issue. However, Section 6 reports on recent data showing modulatory actions of corticosteroids on cognitive processes sustained by the amygdala.

4. Effects of adrenal steroids on animal cognition

The hippocampus is a structure that serves a critical role in memory formation (for reviews, see [174,175]), and it has been suggested that the corticosteroid modulation of hippocampal activity may underlie some aspects of the acute effects of corticosteroids observed in animal learning and memory processes. The effects of adrenal steroids on animal cognition and its neural substrate have been studied using, for the most part, three types of models that tap into hippocampal function.

(1) The first approach is to examine the neuroendocrine modulation of a physiological model of neuronal excitability that is relevant to memory. As previously described (see Section 3.4), hippocampal long-term potentiation (LTP) describes a long-lasting enhancement in synaptic efficacy that occurs in response to high-frequency electrical stimulation [109,181]. Long-term potentiation shares many characteristics in common with memory, the most important being its rapid induction and its long duration.

(2) The second approach is through the measure of associative learning, as defined by various aspects of conditioning behaviors. Passive avoidance learning, acquisition of immobility response, and other associative learning paradigms consist of having an animal learn the association between two stimuli. In order to do this, the animal must integrate different components of the training experience and the effects of different drugs, given at different stages of the learning process, can thus be measured.

(3) The third approach is through the study of spatial memory. Spatial orientation and spatial memory are sensi-

tive to hippocampal lesions [84,139]. Many forms of mazes (radial maze, T-maze, Morris water maze) are used in order to measure the effects of adrenal steroids on animal cognition. In all these instances, a deficit in spatial memory is defined as a failure to remember previously visited arms in the maze, due to some type of treatment.

In each of these approaches, the effects of corticosteroids on behavior are measured using two general research strategies. First, corticosteroids can in some case reverse the positive or negative effects of various drug or surgical treatments (modulatory effects). Second, corticosteroids can by themselves induce positive or negative cognitive changes when acutely administered (direct effects). Within the range of studies on the direct effects of corticosteroids on cognitive function, corticosteroids effects on cognition have been shown to be dose- and/or time- and/or receptor-type-dependent. Table 3 (set A–E) describes the studies performed in each of these fields of investigation.

4.1. Modulatory and direct effects of corticosteroids on neural excitability and cognition

A number of studies have reported that the induction of LTP in the hippocampus is blocked by the administration of corticosterone [56,61]. The role of corticosteroids in hippocampal LTP have further been confirmed by studies showing that the acute administration of corticosteroids in the dentate gyrus of the hippocampus produces LTP [61,144]. In 1991, Bennett and collaborators [13] reported the existence of a negative correlation between the magnitude of LTP in the CA1 population spike in the hippocampus and the level of circulating corticosteroids, thus suggesting a dose-dependent relationship between corticosteroids and their detrimental effects on LTP. One year later, Diamond and collaborators [54] showed that the relation between corticosteroids and LTP follows more closely an inverted-U shape relationship than a negative linear relation. They described a positive correlation between corticosterone and primed burst potentiation (PBP; which is a low threshold form of LTP; [13]) at low levels of corticosteroids and a negative correlation between corticosterone and PBP at high levels of corticosteroids. These results provided a strong support for the hypothesis that corticosteroids exert a concentration-dependent biphasic influence on LTP.

Removal of the adrenal glands has detrimental effects on behavior and many authors have tried to reverse these negative effects by administering glucocorticoids. Using this paradigm, many have reported that pre-training [122,123,132], as well as post-training [23,53,132,189] administration of corticosterone restores an impaired learned behavior or extinction pattern induced by an adrenalectomy. Veldhuis and collaborators [187,188] have further shown that pre-training administration of corticosterone blocks the reduction in the pattern of exploratory behavior observed after an adrenalectomy. Because modulation of cortisol levels gives rise to a concomitant modulation of the learning and memory processes, direct implication of corticosteroids in memory function were postulated.

Such direct effects of corticosteroids on associative learning paradigms were described and the majority of them revealed negative direct effects of corticosteroids on animal cognition. For example, acute administration of either corticosterone or dexamethasone accelerates the rate of extinction of a shock avoidance response [20,21,70,163]. Similarly to studies performed on LTP, it has been shown that the effects of corticosteroids on animal cognition follow an inverted-U shape relationship [94]. In 1976, Kovacs and collaborators [94] reported that low doses of corticosterone facilitate extinction of an avoidance response, while high doses of corticosterone delay the rate of extinction of the conditioned response.

Biphasic modulatory effects of corticosteroids were also reported using spatial memory paradigms. Acute corticosterone administration restores the spatial memory deficit induced by adrenalectomy in adult rats [112]. Moreover, the administration of corticosterone to very young rats impairs spatial memory [47] and this effect is dose-dependent [190]. A completely different effect in the spatial memory performance of young rats is however observed if the corticosteroid is given to the dams, from the day after delivery to the weaning period. In this case, circulating corticosterone levels are decreased in the pups, and spatial memory performance is increased compared to controls [37].

The demonstration of an inverted-U shape relationship between corticosteroids and LTP and associative forms of memory led to the question of whether the involvement of corticosteroids in memory processes involves opposing or synergistic processes that could be mediated by the two types of adrenal steroid receptors reported to exist in the hippocampus and other brain regions.

4.2. Differential effects of steroid receptors activation on neural excitability and cognition

To test this hypothesis, Pavlides and collaborators [145] used Type I and Type II agonists and antagonists, alone or in combination with each others, and measured LTP in the dentate gyrus of the hippocampus (see Table 2, set E). The results showed that the inverted-U shape relationship previously described by Diamond et al., [54] may be explained by a differential activation of Type I and Type II adrenal steroids receptors in the hippocampus. In their study, the activation of Type I receptors led to an increase in LTP while the activation of Type II receptors led to a decrease in LTP. Both these effects were blocked by the administration of their specific antagonist. Similar inhibitory actions of Type II receptor antagonists on the population spike amplitude of hippocampal slice preparations were also obtained using RU 486 [156,157,179].

Table 3
Review of the studies performed in animal populations that have measured the effects of corticosteroids on cognition

Set A: glucocorticoids as modulators of cognitive effects

Type of process	Compound	Dose and method	Time	Population	Effect	Reference
LTP	5-dihydrocortico-sterone	1 mg/ml injection	post-LTP	ADX anaesthetised	blocks the induction of LTP in the hippocampus	[56]
	aldosterone	1 mg injection	post-LTP	ADX anaesthetised	blocks the induction of LTP in the hippocampus	[61]
Associative	corticosterone	5 mg/ml injection	pre-training	ADX	restores the enhanced extinction rate induced by ADX	[122]
	dexamethasone	40 μg/0.2 ml	pre-training	ADX	no effect	[123]
	corticosterone	300 μg/100 g injection	pre-training	ADX	restores the reduced exploration induced by ADX	[187]
	aldosterone	30 μg/100 g injection	pre-training	ADX	no effect	[188]
	corticosterone	30 μg/100 g injection	pre-training	ADX	blocks the efficacy of adrenaline to improve an impaired avoidance response	[50]
	dexamethasone	equimolar	pre-training	ADX	no effect	
	aldosterone	equimolar	pre-training	ADX	no effect	
	corticosterone	30 μg/100 g injection	post-training	ADX	restores the abolishment of a forced extinction response induced by ADX	[23]
	dexamethasone	30 μg/100 g injection	post-training	ADX	no effect	
	dexamethasone	μg range pellet	post-training	ADX	restores the impaired retention of an immobility response induced by ADX	[53] [189]
	corticosterone	1 mg/kg injection	pre- or post-training	ADX	restores the impaired retention of an immobility response induced by ADX	[132]
	dexamethasone	0.3–1.0 mg/kg	post-training	intact	restores the impaired inhibitory avoidance response induced by ADX	[163]
Spatial	corticosterone	20 μg/ml drinking water	5 days pre and 5 days within training	ADX	restores the impairment of spatial memory induced by ADX	[112]

Set B: Glucocorticoids as direct inducers of cognitive effects

Type of process	Compound	Dose and Method	Time	Population	Effect	Reference
LTP	corticosterone	40 mg/kg injection	post-LTP	intact anaesthetised	decreases LTP in the dentate gyrus	[144]
Associative	cortisol	implanted [1]			accelerates the rate of extinction of a shock avoidance response	[20] [1]
	corticosterone	implanted [1] 0.2–1 mg [2]	post-training	intact ADX [1]		[21] [1]
	dexamethasone	2.5–5.0 μg [1]				[70] [2]
	corticosterone	0.4 ml injection	post-training	ADX	no effect on the rate of extinction	[122]
	corticosterone	0.1–4 mg/kg	post-training	intact	no effect	[68]
	corticosterone	5 mg/day	post-training	intact	no effect	[44]
		10 mg/day	post-training	intact	potentiates fear conditioned response	
	dexamethasone	0.3–1 mg/kg	Post-training	intact	increases inhibitory avoidance response	[163]
Spatial	corticosterone	200 mg/3 weeks pellet	pre-training	intact young	impairs spatial memory	[47]
	corticosterone	200 μg/ml drinking water	pre-training	intact dams	improves spatial memory in the progeny	[37]

Set C: glucocorticoids as dose-dependent inducers of cognitive effects

Type of process	Compound	Dose and Method	Time	Population	Effect	Reference
LTP	–	–	–	–	–	–
Associative	corticosterone	1 and 5 mg/kg injection	post-training	intact	facilitates extinction of an active avoidance behavior	[94]
		10 mg/kg injection	post-training	intact	delays the rate of extinction of active avoidance behavior	
Spatial	dexamethasone	1 mg/kg injection	pre-training	intact young	impairment of spatial memory	
		100 mg/kg injection	pre-training	intact young	larger impairment in spatial memory	[190]
	corticosterone	0.2–40 mg	pre-training	ADX	quadratic function curve between Type II receptor occupancy and spatial memory performance	(Conrad et a

Set D: glucocorticoids as time-dependent inducers of cognitive effects

Type of process	Compound	Dose and Method	Time	Population	Effect	Reference
LTP	corticosterone	40 mg/kg injection	2 h post-LTP	intact anaesthetised	decreases LTP in the dentate gyrus	[144]
			24 h post-LTP		no more effect	
Associative	Type I antagonist (RU28318)	0.25, 1, 2 ng; injection	pre-training	intact chick young	30 min post-injection: no effect	[167]
					4 h and 24 h post-injection: impairment in learning	
			post-training		no effect	
	Type II antagonist (RU38486)	0.25, 1, 2 ng; injection	pre-training	intact chick young	30 min post-injection: no effect	
					4 h and 24 h post-injection: Inverted-U shape curve between dose	
			post-training		and decrease in memory no effect	
Spatial	dexamethasone	5–8 mg/kg injection	post-training	intact	if administered up to 150 min post training: increases spatial memory	[62]
					if administered after 210 min post-training: no effect	

Set E: glucocorticoids as receptor-type-dependent inducers of cognitive effects

Type of process	Compound	Dose and Method	Time	Population	Effect	Reference
LTP	Type I agonist (aldosterone)	100 μg/kg injection	pre-recording	ADX anaesthetised	enhances LTP in the dentate gyrus	[145]
	Type I antagonist (RU28318)	50 mg/kg injection	pre-recording	ADX anaesthetised	abolishes the aldosterone enhancement of LTP	
	Type II agonist (RU28362)	100 μg/kg injection	pre-recording	ADX anaesthetised	decreases LTP in the dentate gyrus	
	Type II antagonist (RU38486)	7.5 mg/kg injection	pre-recording	ADX anaesthetised	abolishes the RU28362 decrease in LTP	
	Type II agonist (RU28362)	40 μg/kg	post-LTP	ADX anaesthetised	produces a long-term depression in the dentate gyrus	[146]
Associative	Type II antagonist (RU38486)	2.5 mg/100 g injection	pre-training	intact	reduces duration of the immobility response	[189]
	Type I antagonist (RU28318)	0.25, 1, 2 ng; injection	pre-training	intact chicks young	alters reactivity to non-specific aspects of training	[167]
	Type II antagonist (RU38486)	0.25, 1, 2 ng; injection	pre-training	intact chicks young	impairs consolidation process of a passive avoidance response	
	Type II antagonist	1–10 mg/kg	pre-training	intact	attenuates retention of acquired immobility response	[53]

Table 3 (continued)

Set A: glucocorticoids as modulators of cognitive effects

Type of process	Compound	Dose and method	Time	Population	Effect	Reference
Spatial	Type I antagonist (SC9420)	100 ng/μl Intracranial	pre-training Session 1 (acquisition and consolidation)	intact	impairment in performance on Morris water maze	[138]
			post-training Session 1 (consolidation)		impairment in performance on Morris water maze	
			pre-session 2 (retrieval)		no effect	
	Type II antagonist (RU38486)	100 ng/μl intracranial	pre-training Session 1 (acquisition and consolidation)	intact	no effect	
			post-training Session 1 (consolidation)		no effect	
			pre-session 2 (retrieval)		no improvement	
	Type I agonist (Aldosterone)	100 μg/kg	pre-training (Acquisition and consolidation)	ADX	restores memory impairment induced by ADX	[42]
			post-training (immediately after training)	ADX	restores memory impairment induced by ADX	
			post-training (immediately before recall)	ADX	restores memory impairment induced by ADX	
	Type II agonist (RU28362)	40 μg/kg	pre-training (Acquisition and consolidation)	ADX	no effect	
			post-training (immediately after training)	ADX	no effect	
			post-training (immediately before recall)	ADX	restores memory impairment induced by ADX	
	Type I antagonist (RU318)	30 mg/kg	pre-training	intact	memory performance not different from that of sesame-treated rats	(see Conrad et al., unpublished results)
	Type II antagonist (éru555)	30 mg/kg	pre-training	intact	memory performance significantly lower than that of sesame-treated rats	

Moreover, a second study performed by Pavlides and collaborators [146] showed that the decrease in LTP observed in the dentate gyrus after activation of Type II receptor could in fact be described as the induction of a long-term depression, showing that corticosteroids can have potent delayed suppressive effects on hippocampal plasticity. These authors have suggested that this long-term depression observed after Type II corticosteroid receptors activation in the hippocampus may provide an explanation for the behavioral deficits seen with elevation of glucocorticoids in animal and humans.

Differential effects of Type I and Type II receptor inactivation on the behavior of intact rats were also measured using spatial memory paradigms and interesting qualitative differences were reported on the process of memory formation. In order to provide a basis for discussing the relationship between corticosteroids and memory, we will assume that memory processing involves at least three stages. The acquisition period is the time when the individual acquires the knowledge to be remembered. At this time, the relevant information coming from the environment in which the learning process occurs must be integrated adequately for the information to be correctly acquired. It is at this time period of the learning process that functions such as arousal, attention, and sensory integration must come into play for the information to be acquired. The retrieval situation is a later time at which it would be adaptive for the acquired knowledge to be activated and utilized by some information process. Here again, functions such as arousal and attention may come into play in order to retrieve the correct information. The retention interval is the time period that passes between the acquisition period and the retrieval situation, and serves to strengthen the consolidation of the memory trace.

Memory consolidation is a dynamic feature of long-term, declarative memory, which suggests that memory is not fixed at the moment of learning but continues to develop with the passage of time. Consequently, memory is also susceptible to disruption by internal (arousal, attention) of external events during this period. Studies in animals and humans have shown that, if undisrupted, memory for one-trial experience persists for at least 12 weeks in mice, while in humans, memory for specific information can persist for more than 16 years, and yet it still remains susceptible for disruption for a few years after initial learning [174]. However, a linear decrease of memory with increase in retention interval between acquisition and recall is observed, in both animal [15,64], and humans [83,204], and this describes one cause of forgetting from long-term memory, i.e., a decay of the learned information with the passage of time. However, another cause of forgetting from long-term memory is interference. In this case, forgetting occurs because memory is obliterated or masked by other information or events (e.g., drug or surgical treatment, stress, concomitant event at the time of learning). Fig. 1 presents a schematic representation of

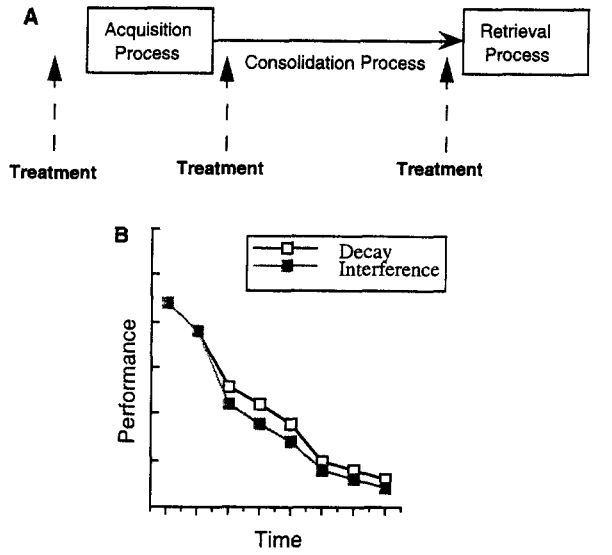

Fig. 1. A: schematisation of different processes involved in memory formation and of differences in treatment administration to assess drug effect on each process. B: schematisation of the effects of decay and interference on the forgetting process.

these three memory processes along with a curve depicting the time course of forgetting due to decay or interference.

Various treatments can affect one or more of these three steps. In the animal literature, most studies on the effects of treatment on memory processes originally applied the treatment each day before training the animal (see Fig. 1). Supposedly, the effect of treatment on acquisition of information was being assessed. However, a significant effect of treatment on memory was not a proof that the agent specifically affected memory since processes such as attention, arousal and motivation could also be affected by the agent, which would eventually lead to a lower level of acquisition and, then, a lower recall. A methodological improvement involves administering treatment immediately after training [124,125], thus giving an indication of the effect of treatment on consolidation and recall, or shortly before recall, giving an indication of the effect of treatment on recall process.

Oitzl and De Kloet [138] were the first to study the effects of corticosteroids on these different processes of memory formation using Type I and Type II corticosteroid antagonists. They described complicated effects of adrenal steroids on spatial navigation in the Morris water maze, and we summarize their experiments and results. Separate groups of intact rats were either administered Type I or Type II antagonists (see Table 3, Set E for the specific compounds used). Antagonist administration was either given before training the animal in the Morris water maze for the first time (pre-training/session 1) or after training the animal in the Morris water maze for the first time (post-training/session 1). Other rats received the antagonist administration before being measured in the Morris water maze for the second time (pre-session 2). In this way, it was possible to measure the effects of cortico-

steroid antagonists on the acquisition and consolidation processes of memory (when the rats were injected before being confronted with the maze for the first time; pre-training/session 1), or their specific effect on the consolidation process itself (when the rats were injected after having been confronted with the maze for the first time; post-training/session 1). Finally, by injecting the corticosteroid antagonists into another group of rats that had already learned (acquired and consolidated) the maze on a first occasion (pre-session 2), it allowed the researchers to measure the effects of corticosteroid antagonists on the retrieval process.

The results of this study are summarized in Table 3, Set E. The authors reported that the administration of Type II antagonist impaired the performance of the rats that were injected before and after their first session in the water maze, but did not affect the performance of the rats that were injected before performing in the maze for the second time. In other words, when the animal was acquiring and/or consolidating the task, Type II antagonist administration had a detrimental effect on their performance. Once the animal had acquired and consolidated the task, Type II antagonist administration had no longer any effect on performance. This led the authors to conclude that Type II receptors are involved in the process of memory consolidation. On the contrary, the administration of Type I antagonist had no effect on performance of the rats that were injected before and after their first session in the water maze, and did not improve the performance of the rats that were injected before performing in the maze on a second occasion.

Interestingly, the control and Type II antagonist-treated rats improved their performance when tested on a second and third occasion (practice effect), showing that they were able to use the search/escape strategies previously adopted during session 1 in order to explore the maze efficiently on a second occasion. Rats treated with Type I antagonist were not able to use these previous search/escape strategies to improve their performance (but did not either show a decline in performance, which eliminates a possible memory deficit). A subsequent experiment performed by Oitzl and De Kloet showed that in fact, these rats spent more time swimming around the maze than the other rats, which led the authors to suggest that Type I receptor may be involved in the process of evaluating the situation and selecting an appropriate response (sensory integration).

Two years later, Sandi and Rose [167] reported similar data using an associative learning paradigm with young chicks. They showed that the administration of either Type I or Type II receptors antagonists decreased associative learning performance, but in a qualitatively different way (see Table 1, Set D). They first reported that the administration of Type I or Type II receptor antagonists before the learning phase did not affect retention when measured 30 min after drug treatment but had a detrimental effect when measured 4 h and 24 h later. The reduction of performance following pre-training administration of the antagonists could have affected all three processes of memory (acquisition, consolidation, and by extension, the recall process). In order to measure a possible differential effect of Type I and Type II receptor antagonists on recall of information, they injected the antagonists 5 min after having trained the animal on the passive avoidance task. Neither antagonists affected the recall process. Finally, in order to discriminate the effects of the antagonists on the strategies of evaluation of the learning situation (during the acquisition phase), they administered the antagonists and then measured various aspects of behavior related to the associative learning task. They showed that chicks injected with Type II antagonist showed a similar behavioral pattern as chicks injected with saline, while those injected with Type I antagonist showed an increase in reactivity to their surroundings (increase in approach behavior and pecking). They concluded that Type I receptor antagonist altered the chicks' reactivity to non-specific aspects of training (i.e., learning procedures used in the acquisition phase) while Type II receptor antagonist affected the acquisition of the passive avoidance response, through the consolidation process (because of the time effect observed by the authors with pre-training administration of the antagonists).

More recently, and using a paradigm in which spatial memory and exploratory behavior can be measured concomitantly, Conrad and collaborators [42] obtained data going along with such a hypothesis. They investigated the modulatory actions of Type I or Type II adrenal steroid agonists on ADX rats' performance in the Y-Maze at three different time points (120 min prior to learning, immediately after learning, or 120 min after learning). The results indicated that treatment with Type I agonist restored the memory capacities of ADX rats to a level comparable to Sham-treated rats by acting on acquisition and consolidation, whereas treatment with Type II agonist did not change the poor spatial recognition memory performance of ADX rats. A detailed analysis of exploratory behavior showed that both the Type I and Type II agonist treated rats were more explorative than the ADX and Sham groups at all periods of the experiment. These results show that the non-specific increase in exploratory behavior induced by corticosteroid treatment was used differentially by the Type I and Type II agonist treated rats to learn and consolidate spatial information. Type I agonist-treated rats efficiently used this increase in exploratory behavior to correctly learn and consolidate the information, while the increase in exploratory behavior induced by the administration of Type II agonist interfered with the learning and consolidation of the information in these Type II agonist treated-rats.

The same group of researchers extended these results in a second study [43] in which they measured performance in the Y-Maze of intact rats administered with either Type I or Type II receptor antagonists. The results showed that

the only group showing impaired spatial memory performance was the Type II antagonist treated group, while the Type I antagonist treated rats performed as vehicle-injected rats. This led the authors to suggest that if an inverted-U shape curve explains the results obtained with memory performance at difference doses of corticosterone, it may only be related to Type II receptor activation. In order to test this hypothesis, they gave different doses (ranging 0.2–40 mg) corticosterone to ADX rats and determined Type I and Type II receptor occupancy using binding assay technics. Type I and Type II receptor occupancy was then correlated to spatial memory performance on the Y-Maze using polynomial regression analyses. The results showed that the level of Type II receptor occupancy was significantly correlated to spatial memory performance following an inverted-U shape curve function, while the level of activation of Type I receptor was not. These results suggest that, not only differential effects of Type I and Type II receptor activation may be related to differences in cognitive performance, but also that different shape functions may exist for each type of receptors occupancy with regard to its relation with cognitive performance.

Other studies have provided important supplementary data for dissociating steroid effects on different aspects of memory formation and recall. In 1981, Micheau and collaborators [127] examined the possible central effects of glucocorticoids on memory consolidation by injecting the drug immediately after the acquisition period. They showed that glucocorticoid treatment is ineffective in a continuously reinforced operant conditioning task, while it facilitates retention when one uses a discriminative operant conditioning procedure. They later reported that the glucocorticoid treatment is still effective when given within 6 h after the acquisition period [125]. In 1991, Mitchell and Meaney [132] showed that the effects of adrenalectomy on the acquisition of an immobility response were entirely reversed by a 1 mg/kg dose of corticosterone, only when the steroid was present during both the training and testing phases. They interpreted these results as showing that corticosterone affected the consolidation process and that this effect occurs under basal levels of corticosterone and did not require elevated glucocorticoids levels associated with stress. A complementary interpretation was however proposed by De Kloet and Reul [153] in their thorough review of the action of corticosteroids on brain function. They suggested that "...while for consolidation of the passive avoidance response, CORT does not seem to be required, (...) the presence of CORT is essential for proper interpretation of the environment" (p. 92). In light of the more recent data on differential effects of Type I and Type II receptor blockade [138,167] (see also [43]) it seems that both interpretations were accurate at the time and may have depended on the dose used by the authors to observe the acute effects of corticosterone on animal behavior.

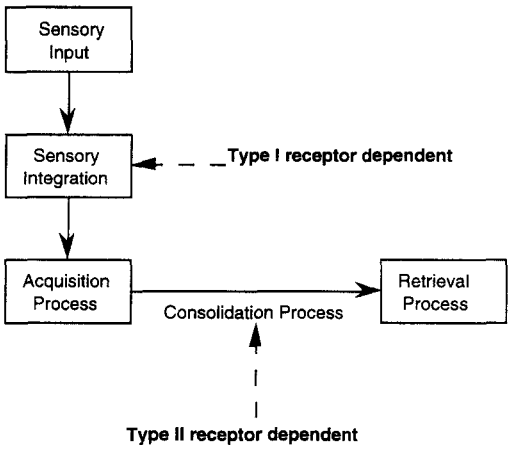

Fig. 2. Schematisation of the effects of corticosteroids on animal cognition with a particular emphasis on Type I and Type II adrenal receptor activation.

Taken together, these results suggest that the dose-dependent relationship previously observed between corticosteroids and memory process in the animal may in fact be explained by the differential activation (or blockade in the case of antagonist administration) of Type I and Type II adrenal steroid receptors, particularly in the hippocampus. Type I receptor activation may be implicated in the process of memory formation through the process of sensory integration. In this phase, the animal must select the relevant information in the environment that will facilitate the acquisition of information. In contrast, the activation of Type II receptor is thought to be related to the process of acquisition and consolidation of the memory trace. The time-dependent effects of Type II corticosteroid receptors activation on animal behavior [62,167] goes along with such a suggestion. Fig. 2 presents a schematization of the effects of corticosteroids obtained in the animal literature.

5. Effects of adrenal steroids on human cognition

Let us go on to see how this analysis of opposing and/or multiple actions of adrenal steroids fits the human literature. Here again, time and/or dose-dependent effects of corticosteroids on cognition have been described. Moreover, non-specific (arousal/attention) and specific (memory) effects of corticosteroids have been obtained and the data have served to strengthen the view about the role of corticosteroids in the process of sensory integration, and memory processes such as acquisition and consolidation.

The first area of investigation in the last three decades has been the study of the effects of exogenous corticosteroids upon psychophysical processing of stimuli. This field of research was developed after the observation made by Henkin [76] that patients with adrenocortical insufficiency show increased sensory detection, and that treatment with carbohydrate-active steroids return detection

Table 4
Review of the studies performed in human populations that have measured the effects of corticosteroids on cognition: glucocorticoids as direct inducers of cognitive effects

Type of process	Compound	Dose and method	Time	Population	Effect	Reference
Arousal	hydrocortisone	20 mg oral	pre-training	males	decreases auditory tonal detection (hypoarousal)	[12]
	hydrocortisone	16 mg infusion	during	males	reduces the amplitude of the evoked potential component related to arousal (hypoarousal)	[25]
	hydrocortisone	50 mg oral	pre-training	males	decreases taste detection (hypoarousal)	[59]
	hydrocortisone	50 gm infusion	pre-training	males	increases auditory sensitivity (hyperarousal)	[27]
	hydrocortisone	20–40 mg infusion	pre-training	males	inverted-U shape effect on auditory evoked potentials	[26]
Selective Attention	hydrocortisone	3 mg/kg infusion	during	males	decreases selective attention	[93]
Memory	hydrocortisone	5,10,20,40 mg; oral	pre-training	males	all doses increase memory but only the highest dose continue to do so with practice	[12]
	hydrocortisone	10 mg oral	pre-training	males	decreases declarative memory but do not affect non-declarative memory	[91]
	hydrocortisone	40,300,600 μg/kg infusion	during 4 h post 4 days	males	no effect during the infusion but a 4th day poorer recall of the post information learned during the infusion	[105]
	prednisone	80 mg/5 days oral	pre-training	males	affects recognition of previously presented words	[197]
	dexamethasone	1 mg oral	pre-training	males	no effect	
	dexamethasone	0.5 and 1 mg/daily 4 days oral	pre-training	young males	impairs declarative memory on the 4th day of treatment	[136]
	dexamethasone	1,2,3,4 mg/daily 4 days oral	pre-training	young aged	impairs declarative memory immediately and at the 4th day of treatment. no effect	[137]
	hydrocortisone	50 mg morning and night	pre-training	young males	suppresses the circadian variations observed in cognitive function (higher free recall in the morning)	[60]

thresholds to normal limits. Although a lack of glucocorticoids seemed to increase sensory acuity, it was shown later to be associated with a deficit in the integration of sensory information, i.e., patients with untreated adrenocortical insufficiency were less able to correctly recognize acoustically presented words, and performance returned to normal after glucocorticoids treatment. Henkin [76] concluded from these findings that glucocorticoids impair sensory acuity whereas perceptual integration may be improved. The second area of investigation evolved after the discovery of adrenal steroid receptors in the hippocampus and is mainly concerned with the effects of synthetic glucocorticoids on the process of memory. Contrary to the animal literature, the effects of glucocorticoids on human cognition have rarely been evoked using modulatory influences of corticosteroids on behavior. Instead, the direct effects of corticosteroids have been consistently measured, and just as for the animal data, dose- and time-dependent effects have been reported (see Table 4).

5.1. Non-specific effects of corticosteroids on arousal and attention

The first published observation of the acute effects of corticosteroids in healthy humans was made by Kopell and collaborators [93] who found negative influences of an acute cortisol infusion (3 mg/kg body weight) on the latency of the visual evoked potential and on time estimation. They concluded from these results that cortisol may have slowed the rate of an internal clock (hypoarousal) and decreased the subjects' ability to attend differentially to certain visual stimuli (selective attention). This suggestion was further supported by studies using auditory evoked potentials [11,26], and taste detection paradigms [59].

Interpretations drawn from glucocorticoid-induced changes in threshold detection in Addison's patients [76], and in evoked-related potentials in normal controls [11,26,59,93] assumed either an effect on non-specific, arousal-related aspects of stimulus processing or an effect on selectivity of attention. In an attempt to differentiate between these two processes, Born and collaborators [25] studied different aspects of stimulus processing (arousal, selective attention) as indicated by evoked-related potentials components recorded in a dichotic listening paradigm. They showed that a 2 h infusion of a 16 mg dose of hydrocortisone leads to a reduction in the amplitude of the evoked potential component related to cortical sensitivity (arousal), but to no difference in the selective attention component of the evoked potentials. They thus concluded toward an inhibitory action of enhanced plasma cortisol levels on stimulus processing mediated by the non-specific sensory system (hypoarousal).

However, studies in which evoked potentials were used to assess central nervous effects of glucocorticoids did not unequivocally support an hypoarousal effect. Born and collaborators [26] found enhanced amplitudes of the auditory vertex potential components during high plasma cortisol concentrations following a 2 h administration of 20 or 40 mg of hydrocortisone. In an attempt to differentiate between the hypo- and hyperarousal effects of glucocorticoids, these authors [27] studied whether a 20 min hydrocortisone infusion of 50 mg affects early sensory processing as reflected by auditory brain-stem response when the subjects is confronted with different stimulus intensities and stimulus rates. The results showed that cortisol induced specific changes in human auditory brain-stem responses depending on the particular characteristics of the stimulation condition. At low intensities, the auditory brain-stem responses were notably reduced following glucocorticoid administration, whereas no changes in auditory brain-stem responses were observed at high intensities following glucocorticoids administration. The authors interpreted their results as showing that glucocorticoids exert different influences at different stages of sensory processing. Similar effects of glucocorticoids on sensory processing were reported by Beckwith and collaborators [11] who showed that a 20 mg administration of hydrocortisone 1 h before testing leads to a reduction of auditory sensitivity only for high frequency tones, while no such effect is observed for low frequency tones.

5.2. Specific effects of corticosteroids on memory

Although most of the early attempts to explore the effects of glucocorticoids upon human brain functioning were published in the psychophysical literature, it is memory that became the cognitive process of choice in the early 1980's. Although the infusion of hydrocortisone was the experimental paradigm mostly chosen by researchers measuring the influence of corticosteroids on brain excitability, it is the oral administration of either hydrocortisone, dexamethasone or prednisone that attracted researchers interested in the measure of the influence of corticosteroids on memory function.

Interestingly, the first study performed on the acute effects of corticosteroids on human memory process was a dose-response study. In 1986, Beckwith and collaborators [12] tested the effects of exogenous administrations of 5, 10, 20 and 40 mg of hydrocortisone on short and long term memory. Sixty minutes after the oral administration of hydrocortisone, subjects were given the task of memorizing short lists of words and tested after each list for their ability to recall the items. The results of the study showed that the effects of hydrocortisone on human memory performance depend upon the dose administered and the amount of practice given on the memory task. Thus, all doses facilitated recall of words during the first presentations of lists, while only the highest doses of hydrocortisone (40 mg) continued to enhance recall when subjects were presented with more lists of words. The 5 mg dose retarded performance with increasing practice. Since hydrocortisone did not directly interact with memory perfor-

mance, the authors interpreted their results as being related to motivational/arousal changes rather than to a specific enhancement of memory function.

However, a more recent study reported a different pattern of results using a very similar protocol. Kirschbaum and collaborators [91] showed that the oral administration of 10 mg. of hydrocortisone leads to a significant decrease in memory performance as tested 60 min after hydrocortisone intake. In their study, they measured declarative and non-declarative memory performance in order to assess the influence of corticosteroids on hippocampal formation process. The logic for the inclusion of this mnesic dissociation is due to the fact that studies report that the hippocampus is essential for a specific kind of memory, notably declarative [41], while it is not essential for non-declarative memory [33,40,65,80,171,173,174,182]. Declarative memory refers to conscious or voluntary recollection of previous information, whereas non-declarative memory refers to the fact that experience changes the facility for recollection of previous information without affording conscious access to it (priming). Thus, this somewhat specialized role of the hippocampus serves as the basis for specific hypotheses regarding the effects of acute administration of corticosteroids on human cognition [103,136]. The results showed that subjects who received hydrocortisone treatment presented an impaired performance in the declarative memory task but not in the non-declarative memory task, thus suggesting that cortisol interacts with hippocampal neurons to induce cognitive deficits.

The discrepancy between Beckwith's study (who found no influence of a 10 mg administration of hydrocortisone but an increase in memory performance at higher doses) and Kirschbaum's study (who found detrimental effects of a 10 mg administration of hydrocortisone) may stem from the fact that in his study, Beckwith used glucose administration as a placebo condition and mixed the hydrocortisone with glucose for treatment effect. Many studies have reported increased cognitive efficiency after glucose administration [14,92,142,143], and this fact could explain the positive effects obtained by Beckwith, when compared to Kirschbaum and collaborators who used matched placebo capsules.

Besides acute actions, delayed effects of glucocorticoids were reported in memory studies on human subjects. Wolkowitz and collaborators [197,198] observed impaired memory performance in normal adults following 5 days administration of high doses of prednisone (80 mg p.o. daily), but normal memory performance in another group of subjects following a more acute administration of 1 mg of dexamethasone. One week before drug administration, subjects were presented with a list of semantically related words and asked to immediately recall them. On the day after drug administration, subjects were presented with a list of words which contained the previously learned words (targets), as well as other words never presented to the subjects (distracter words) and their task was to recognize the previously presented words. The results showed that the administration of prednisone led to an increase in incorrect detection, while the administration of dexamethasone did not have any effect. The general cognitive deficit that the authors described in this study involved the relative inability to discriminate previously presented relevant information (target) from irrelevant information (distracters) in a test of recognition memory. They concluded that exogenous administration of corticosteroids may have diminished the encoding of meaningful stimuli and impaired selective attention, i.e., reducing the ability to discriminate relevant from irrelevant information [185]. They proposed that the corticosteroid-dependent changes observed in memory may be explained by increased arousal, based on the hypothesis of Yerkes and Dodson [202] proposing that an inverted-U shape curve describes the relationship between arousal and cognitive efficiency. In this model, corticosteroids would induce a state of hyperarousal, which would then result in an overselectivity in external input, a decreased use of relevant cues, and an impaired cognitive performance [197].

Results obtained by Fehm-Wolfsdorf and collaborators [60] goes along with this hypothesis. In their study, they measured the effect of an oral administration of 50 mg of hydrocortisone on a free recall task in young normal controls in the morning, when endogenous cortisol levels are at their peak, and at night, when they are at their lowest concentration. In a preliminary study, they had shown that placebo treatment was related to a higher cognitive performance in the morning, compared to night. Their results revealed that hydrocortisone administration suppressed the increased cognitive performance in the morning, while it had no effect on cognitive performance when administered at night. It can thus be suggested that the high endogenous cortisol levels in the morning corresponded to the peak of the inverted-U shape function between cortisol levels and cognitive performance, and that the administration of hydrocortisone at that time shifted the performance toward a decrease. On the contrary, the administration of the same dose of hydrocortisone in the evening, when endogenous cortisol levels were very low, may not have been sufficient to increase cognitive performance toward the peak of the inverted-U shape function. Repeating the same study with different doses of hydrocortisone given in the morning and at night could yield very interesting data with regard to the inverted-U shape relationship between variations in endogenous cortisol levels, and cognitive performance.

Delayed effects of dexamethasone on cognitive performance have also been obtained. Newcomer and collaborators [136], using a 4 days administration procedure with 0.5, 1, 1, 1/day of dexamethasone in normal controls, reported impaired declarative memory performance (acquisition and recall) on the fourth day of treatment only. No immediate or delayed effects of dexamethasone were observed on non-declarative memory, and selective atten-

tion performance. These results were in accordance with a hippocampal involvement in corticosteroid-related cognitive deficits and argued against a non-specific effect of the steroid on attention and arousal, as proposed by Wolkowitz et al., [197]. However, a recent study performed by the same authors [137] in young and elderly populations and using 4 days treatment with higher doses of dexamethasone (1, 2, 3, 4 mg/day) showed different results. Using such doses, they reported immediate as well as delayed effects of dexamethasone on declarative memory function in the young population. Thus, increasing the dose of dexamethasone induced immediate effects on declarative memory function in the young population. In contrast, the elderly population did not present an immediate, nor delayed impairment in declarative memory performance following dexamethasone treatment. This latter result may be explained by the higher endogenous cortisol levels observed in a large proportion of elderly subjects [104], and by the detrimental effects of such high levels of cortisol on declarative memory function in the elderly [103]. It is thus possible that the aged population of Newcomer and collaborators might have benefit from the decrease in cortisol levels induced by dexamethasone treatment, which would explain the absence of memory impairment in this population.

The studies performed by Newcomer's laboratory showed that high doses of dexamethasone are necessary to induce immediate deficits in declarative memory, and that continuous treatment with dexamethasone are necessary to maintain the deficit. However, a recent dose-response study from one of us (S.L.) [105] have shown delayed effects of an acute infusion of hydrocortisone on declarative memory performance (consolidation). Four groups of 10 normal young controls were infused with either placebo (saline) or one of three doses of hydrocortisone: 40 μg/kg, 300 μg/kg or 600 μg/kg for 100 min. Blood samples were taken before, during and after the infusion. We measured declarative memory using a cued recall task. In this task, subjects are presented with six pairs of semantically related words and six pairs of unrelated words and they are asked to recall one of the word when presented with the other word of the pair. This task has consistently shown mild memory impairment in elderly subjects who present significant elevations of cortisol levels with years [103]. A first list of 12 word-pairs was presented during the 100 min infusion and both acquisition and recall of the words were performed during the infusion. A different list of 12 word-pairs was then presented 4 h after the hydrocortisone infusion and again, both acquisition and recall of the words were performed. Four days after the infusion, the subjects were asked to recall (with the first word of the pair as a cue) the words learned during the infusion and those learned after the infusion. Preliminary analyses performed on the cortisol levels obtained before, during and after the infusion and memory performance (during, 4 h and 4 days after the infusion) revealed that the extent of cortisol response to treatment was significantly related to a fourth-day poorer recall of the information learned during the infusion. Thus, subjects who presented the greatest increase of cortisol levels during the infusion also presented the greatest fourth-day decrease in memory performance for the words that were learned during the infusion. No such correlation was observed for the words learned 4 h after the infusion. These results suggest that the specific effects of corticosteroids on memory may be delayed in time because they weaken the acquisition and consolidation of information learned during the episode of corticosteroid hypersecretion.

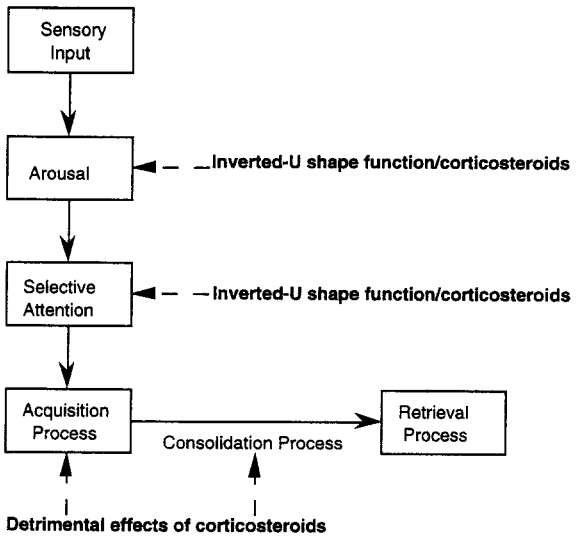

Fig. 3. Schematisation of the effects of corticosteroids on human cognition.

In summary, the results obtained with normal adults suggest that corticosteroids exert an inverted-U shape influence over the processes of arousal and selective attention. Similar modulatory effects of corticosteroids have been obtained on the process of memory, particularly those related to the acquisition (theoretically, this may be occurring through the effects of corticosteroids on arousal and selective attention) and consolidation of the memory trace. Fig. 3 presents a schematization of the effects obtained with corticosteroids on human cognition.

6. Modulatory effects of glucocorticoids on the formation of emotional memory: implications of the amygdala

Although most of the literature on the acute effects of corticosteroids on animal and human cognitive process was reported using the hippocampus as a model for learning and memory, there is now evidence showing that glucocorticoids also act as modulators of the formation of emotional memory in the amygdala. In this section, we report on results suggesting such a modulatory role for glucocorticoids.

There is now extensive evidence that the amygdala is involved in the emotionally influenced processes of learning and memory [28,29,34,74,159,161]. The amygdala contains both Type I and Type II receptors [3,44,100,159,160], and corticosteroid receptors in particular nuclei of the amygdala (particularly the central and medial) have been implicated in emotional expression and in neuroendocrine control of emotions [59,160]. Roozendaal and McGauch [163] showed that lesion of the basolateral and medial nuclei of the amygdala block the dexamethasone-induced memory enhancement in an inhibitory avoidance task, while lesion of the central nucleus of the amygdala does not. These results suggest that the basolateral and medial nuclei of the amygdala are critical sites for glucocorticoid-induced modulation of memory formation for emotional events. More recent data by the same group showed that lesions of the basolateral nucleus of the amygdala also blocks the memory-impairing effect of ADX on the Morris water maze [162]. This later result suggests that the basolateral nucleus of the amygdala may not only be involved in memory for emotional events, but may also be implicated in the modulation of memory storage, through its interaction with glucocorticoids. Consistent evidence for this hypothesis were recently obtained [164]. Bilateral lesions of the stria terminalis, the major afferent-efferent pathway of the amygdala, do not impair performance on an inhibitory avoidance learning tasks and on the Morris water maze, but block the effects of ADX and dexamethasone administration on memory for both tasks. These findings suggest that the integrity of the afferent-efferent pathways of the amygdala to other brain structures is essential for the modulating effects of glucocorticoids on memory storage.

7. Integration of animal and human data

The studies performed with human populations revealed specific effects of glucocorticoids on the process of arousal and/or selective attention, as well as on memory function (particularly the acquisition and consolidation processes of declarative memory function). It is tempting to relate these observed effects to those hypothesized to result from Type I (sensory integration; perceptual organization) and Type II receptor activation (memory acquisition and consolidation), as inferred from animal experiments.

In humans, inverted-U shape functions are proposed in order to explain the relationship between glucocorticoid levels and the processes of arousal and/or selective attention. These same processes have been shown to be under the influence of Type I adrenal receptor activation in the animal learning studies. Indeed, what has been called 'sensory integration' and 'interpretation of the environment' in the animal literature defines a process very similar to the one that has been called 'selective attention' in the human literature. Oitz and De Kloet [138] described the effects of Type I receptor antagonists as affecting the "processes of evaluation of the situation and response selection" (p. 69), and Sandi and Rose [167] wrote about "the integration of different components of the training experience, including the visual characteristics [of the stimulus]" (p. 1296). In humans, selective attention is defined as the process used by an individual to discriminate, in his/her surroundings, relevant from irrelevant information [185]. This process enables an individual to be aware of his/her surroundings (arousal), and to select the appropriate stimuli in the environment (selective attention/sensory integration) in order to have an adaptive response.

The role of glucocorticoids in a process such as selective attention was proposed by McEwen [113] who suggested that glucocorticoids act to suppress the ability of the hippocampus to filter out behaviorally irrelevant stimuli. This suggestion was based on data showing that hippocampal lesions have greater effects in tasks that maximize interference between present learning and similar prior learning, and in tasks in which correct selection of a response from alternatives is required [195]. This suggestion was also supported by other results showing that glucocorticoids block the improvement in selective attention that follows dorsal noradrenergic bundle stimulation [114]. This view of hippocampal processing also goes along with recent findings showing that hippocampal lesions in rats only interfere with context conditioning and not with cue conditioning [149,150]. The fact that hippocampal lesions affect specifically context conditioning while leaving cue conditioning unaffected suggests that the selection of highly contextual relevant information is an important component of the cognitive process sustained by the hippocampus. A specific role of the hippocampus in selective attention was finally demonstrated by recent studies in the rat which showed that hippocampal lesions affect the process of selective attention, as measured by a 5-choice selective attention task [30].

For the memory process, we have noted the importance of distinguishing between the three main components of the memory function, namely the acquisition, consolidation, and retrieval phases. In humans, detrimental effects of glucocorticoids have been obtained, particularly on the processes related to acquisition and consolidation of the memory trace [105]. These same processes were shown to be under the influence of Type II receptor activation in the animal. In this sense, long-term depression [108] is an excellent example of a Type II receptor-mediated steroid effect that is produced by an electrical stimulation and then lasts quite a while. The suggestion made by Squire [175], that the role of the hippocampus in memory is time limited, would fit such a model of the effects of Type II adrenal steroid receptor activation on the process of memory consolidation.

The study of retrograde amnesia in patients with confirmed hippocampal lesions first led to such a suggestion.

These patients have difficulty recalling the recent past but can recall remote events as well as normal subjects [110]. Also consistent with a time-limited role of the hippocampus in memory is a recent study performed by Zola-Morgan and Squire [207] in monkeys. Monkeys were trained preoperatively on an object discrimination task 16, 12, 8, 4 and 2 weeks before surgery for hippocampal removal. Two weeks after surgery, memory was re-assessed. Unoperated monkeys exhibited normal forgetting, while the operated animals showed temporally graded retrograde amnesia. Specifically, the operated monkeys performed more poorly than the control monkeys on stimuli that were learned 2–4 weeks before the surgery, but did not differ from the control group for the stimuli that were learned long before the operation, at a time when consolidation of the learned information could be successfully completed.

Similar results were also obtained with rats [196]. These results provided evidence for a gradual process of consolidation or reorganization in memory as time passes after learning, and led Squire [175] to suggest that the hippocampal formation is essential for memory storage for only a limited period of time. More recent reviews [57] led researchers to implicate the hippocampus in a specific time-frame of memory consolidation, attributing a role of the hippocampus in 'intermediate-term' process of memory. Thus, a temporary memory trace is established in the hippocampus at the time of learning and the role of the hippocampus then gradually decreases, with a more permanent memory being established elsewhere, possibly in the neocortex (see [175] for a detailed review).

Recent reviews of the literature on hippocampal function and cognition have come to the conclusion that at least two sub-systems must be attributed to hippocampal function; an intermediate-term storage of the information, and a relational processor of that information [57,69]. According to this view, the hippocampus (and related structures) supports intermediate-term storage of individual items, and organizes these memories according to relevant relationships among them. These two processes (selectivity of relevant information, and intermediate-term processing of this information) were shown to be under the influence of Type I and Type II receptors activation in the animal literature. It is thus possible that the discrepancy of data in humans with regard to the immediate versus delayed effects of corticosteroids on memory, as well as the inverted-U shape function curves observed between glucocorticoids and cognitive function in animals and humans, are all related to differences in treatment procedures with regard to cognitive measurement, and to differential activation of Type I and Type II receptors in the hippocampus.

In our attempt at integrating animal and human data, we must take into account the methodological and experimental factors that might explain some discrepancies in both populations with regard to glucocorticoids effects on cognition. We hope that by delineating such factors, we will contribute to a better understanding of the effects of corticosteroids on animal and human cognition. Finally, by suggesting new experimental protocols in humans, based on animal studies, we hope to build the first parts of the bridge linking animal and human studies.

7.1. Use of appropriate neuropsychological tools

In human studies, the choice of appropriate tools for measuring the cognitive changes after corticosteroid administration has not been informed by a theory of how corticosteroids affect cognition. Although traditional psychometric methods permits to assess subjects' performance with regard to a given normality score, this fact in itself does not guarantee their sensitivity and validity. Most importantly, there is often an absence of objective criteria in material selection. For example, we have shown the necessity to dissociate subtle cognitive functions such as acquisition, consolidation and retrieval for the memory process, and between arousal and selective attention for the attentional process. Further dissociations are important to be made, particularly for the memory process, as for example that between explicit and implicit memory, since it has been shown that only the former memory process is sustained by hippocampal function. By exclusively using standardized neuropsychological tests, researchers may use materials that may not be sensitive enough to pick up subtle cognitive deficits as observed after glucocorticoid imbalances. In order to demonstrate this fact, Lussier and collaborators [106] conducted a study on test sensitivity for verbal material and have shown that in normal elderly individuals as well as in brain-damaged patients who complained about having memory problems, score on the declarative memory subtests of the Weschler Memory Scale were all in the normal range for elderly and brain-damaged patients (with a ceiling effect for the elderly patients) while on an experimental declarative memory task controlled for frequency of usage and semantic relatedness, controls did not display a ceiling effect and all patients exhibited a declarative memory deficit to various degrees.

Lupien and collaborators [103] have reported the exact same pattern of results when they correlated the basal cortisol levels of their elderly population with declarative memory performance as measured with the Weschler Memory Scale and an experimentally designed declarative memory test. No correlation reached significance levels when they correlated the basal cortisol levels of their elderly population to the Weschler memory score, while a significant negative correlation was obtained between basal cortisol levels and memory performance on the experimental declarative memory task. It is thus possible that the absence of memory deficits after exogenous administration of corticosteroids may, in some cases, be related to the insensitivity of the testing measures. In order to control this fact, it is necessary to use sensitive neuropsychological measures designed in relation to contemporary theories of

human information processing, and not simply to rely on standardized neuropsychological batteries that may not be sensitive enough to pick up subtle cognitive deficits induced by glucocorticoids alterations.

In the animal literature, researchers have started to distinguish the effects of glucocorticoids on the various stages of the memory process. No such step has yet been taken in human studies. However, it is generally easier to measure these memory stages in humans than in animals (for a review, see [128]). Moreover, in humans, it is possible to vary the nature and the extent of the elaboration applied on the information to be acquired and important information could be gathered with regard to the effects of glucocorticoids on an information that has been highly or poorly elaborated. Finally, the issue of selective attention has come up with humans, and further studies in animal and humans, aiming at measuring the effects of corticosteroids on both selective attention and memory function will be necessary if one hopes to specify the nature (rather than the extent) of cognitive deficits induced by corticosteroids.

7.2. Differences in the effects of dexamethasone and hydrocortisone on cognition

As we have noted in the introduction of the effects of corticosteroids on memory function in human populations, the synthetic steroids used in human studies vary widely and they differ in their ability to gain access to the brain. Dexamethasone has been shown to be a potent long-acting inhibitor of HPA activity and to suppress cortisol levels when measured the day after [36]. So, at the time of cognitive testing, circulating cortisol levels are decreased. However, hydrocortisone, when infused and even when orally administered, will give rise to an increase in cortisol levels [91,105], so that at the time of cognitive testing, circulating cortisol levels are increased. As we have observed, cognitive impairments were reported with both decreases and increases of glucocorticoids levels in humans but data have never been interpreted with regard to this important fact.

The finding that both dexamethasone and hydrocortisone have similar effects on cognitive function while they act differently on cortisol levels would led to suggest that it is the physiological disturbance from homeostasis that induces cognitive impairments, rather than specific directional changes in glucocorticoid levels. However, studies in both animals and humans reported differential effects of dexamethasone and hydrocortisone administration on cognitive function. In the animal, it was shown that corticosterone, but not dexamethasone, results in an increase of ambulatory activity [24]. Veldhuis and collaborators [187,188] reported that corticosterone, but not dexamethasone, blocks the reduced exploratory activity induced by adrenalectomy, and similar effects were reported for the normalization of an extinction behavior in adrenalectomized rats [22,23]. Consonant with the notion of highly specific effects of corticosterone on brain function are the observations by Micco et al., [122,123] who found that corticosterone but not dexamethasone influence the extinction of an appetitive response in adrenalectomized rats. In humans, it was shown that 1 mg of dexamethasone prior to sleep leads to a reduction of the percent of time spent in rapid eye movement (REM) stage and in stage 4 sleep while the infusion of 100 mg of hydrocortisone throughout the night also reduces REM but increases stage 4 sleep [67]. Differential effects of dexamethasone and hydrocortisone were also obtained on taste detection acuity. Fehm-Wolsfdorf and collaborators [59] showed that treatment with 50 mg of hydrocortisone led to a clear decrease in taste detection acuity while treatment with 2 mg of dexamethasone had the opposite effect.

7.3. Mechanisms of action of dexamethasone and implication for human studies

These data are in agreement with animal studies showing that dexamethasone and cortisol act at different levels of the HPA axis. Dexamethasone is taken up by pituitary and peripheral organs like spleen and thymus where it gains access to Type II receptors. In brain, there is less uptake of radioactive dexamethasone [45,52,152,158,191], and only prolonged exposure to fairly high levels of dexamethasone results in occupation of Type II receptors in brain [52,127]. One possible mechanism for the dexamethasone access to peripheral tissues is that cortisol is retarded by cortisol-binding globulin (CBG), while dexamethasone is not. CBG is present in pituitary and spleen, for which there is the clearest evidence for the limited access of cortisol and ready access of dexamethasone to Type II receptors. For the brain, there is no CBG available and cortisol readily penetrates the blood-brain barrier, while dexamethasone does no do so very efficiently. It appears that the structure of dexamethasone makes it less able to penetrate the blood–brain barrier. Early work by De Kloet and collaborators [52] showed its lack of access, and work by Rees and collaborators [152] indicated that dexamethasone may reach the brain by first entering the ventricles. Thus, even when dexamethasone does enter the brain at higher plasma concentrations, it may not reach the same compartments (e.g. neurons) as cortisol.

Another mechanism that governs access of adrenal steroids to target tissues is metabolism by specific enzymes. One of these, 11-beta-hydroxysteroid dehydrogenase (11 HSD) is very active in kidney collecting tubules in regulating the access of cortisol (human) and corticosterone (rat) to Type I receptors. This allows aldosterone, present in much lower concentrations in blood, to access the Type I receptor and exert its critical effects to promote sodium retention by the kidney. 11-HSD is present in brain tissue and in glucocorticoid-sensitive tissues like spleen and thymus, but its activity is at least one-tenth of that in

the brain and 11 HSD does not appear to have the powerful role in these tissues that it has in the kidney collecting tubules [63,96,176].

The necessity of prolonged exposure to dexamethasone for Type II receptor occupancy might explained the delayed effects of lower doses of dexamethasone on memory function reported in Newcomer's study [136]. Moreover, activation of Type II receptors at higher doses of dexamethasone could explain why higher doses of dexamethasone were needed in Newcomer's second study [137] in order to induce deficits in declarative memory function. On the contrary, low-dose dexamethasone treatment reduces endogenous corticosterone secretion and increases availability of Type I receptors [128], a type of 'chemical adrenalectomy'. This fact might help explain the cognitive deficits observed with dexamethasone administrations in humans. Indeed, adrenalectomy has been shown to induce cognitive impairment in animals [21,24] and, knowing this, it is not surprising to observe cognitive deficits after dexamethasone administration in humans. We are tempted to suggest the use of dexamethasone administrations in human studies as a sort of chemical adrenalectomy, and to measure the resulting modulatory effects of glucocorticoids on cognitive function. Using such an experimental protocol, one must postulate that the detrimental effects of dexamethasone on human cognition should be reversed by the subsequent administration of hydrocortisone. Such an experimental protocol would permit to measure the modulatory effects of glucocorticoids on human cognition, using a design similar to that used with animals.

7.4. Dose-response versus receptor-type studies in human populations

Since stress levels of glucocorticoids are needed in order to activate Type II adrenal steroid receptors in the rat, it may be suggested that the inverted-U shaped curves observed between glucocorticoid levels and cognitive function in humans is related to a differential activation of Type I and Type II adrenal steroid receptors. The induction of a 'chemical adrenalectomy' by low doses of dexamethasone, with subsequent replacement of low and high doses of hydrocortisone in humans could lead to very interesting results with regard to differential effects of Type I and Type II adrenal receptors activation on human cognition. Such an experimental protocol in humans would be almost identical to the protocol used by Mitchell and Meaney [132] with adrenalectomized rats.

Because of this knowledge about differential activation of Type I and Type II adrenal steroid receptors in the rat with different doses of glucocorticoids, no researcher interested in the study of the effects of corticosteroids in human cognition should decide upon a dose to be administered without taking these two receptor types into account. Reul and De Kloet [153] have determined that a dose of 1 μg/100 g body weight of corticosterone results in 80% of Type I receptor activation in the rat, while Type II receptors are not occupied. They have also shown that for a 50% Type II receptor activation, doses needed to be increased to 50–100 μg/100 g body weight, and for 95% occupancy, a dose of 1 mg is required (note that stress levels of corticosterone results in an approximately 70% occupation of Type II adrenal steroid receptors). Due to the differential cognitive effects induced by Type I and Type II adrenal receptor activation in the rat, researchers should be aware of the type of receptors theoretically activated in their study and interpret their results accordingly.

7.5. Implications for studies on aging

It has been shown that aging can lead, in a subgroup of individuals, to a significant increase of endogenous cortisol levels [104], and that this increase in cortisol levels is significantly related to a decrease in declarative memory performance [103]. Type I and Type II receptors have been shown to be reduced during senescence (for reviews, see [49–51]), and further studies reported that the decrease in Type II receptors during aging is due to the rise in circulating plasma corticosteroid concentrations. Other studies also reported differential effects of a Type II receptor antagonist on the population spike of hippocampal slice preparations in young and aged mice, i.e., Type II receptor agonist administration induced the classical decrease in the population spike of the young animal, but had no effect on the aged animal [180]. These electrophysiological findings suggest an important Type II-mediated glucocorticoid action on age-related modification of hippocampal function. Behavioral studies in rats also reported age differences with regard to the relationship between corticosterone levels and spatial memory performance. Yau and collaborators [201] reported a positive correlation between corticosterone levels and spatial memory performance in young rats, but a negative correlation between corticosterone levels and spatial memory performance in aged rats. Combined with what is now known about the differential effects of Type I and Type II steroid receptors activation on cognitive function, these results have important implications for further studies on the effects of corticosteroids in aging populations. It is thus clear that the interpretation of data obtained in young adults with exogenous administration of corticosteroids cannot be directly extended to that of aged individuals who show a gradual increase of cortisol levels with time.

Moreover, if one is interested at comparing the effects of corticosteroids in young and aged populations, one will have to take into account the extended cognitive literature showing that the age-related memory declines observed in elderly individuals are mainly the result of decreased or slowed rates of acquisition, as well as decreased efficiency of the retrieval process (see [204]). In the majority of elderly individuals, the forgetting rate is not different from

that of young individuals [16,46,101,133,165,183]. Indeed, a higher rate of forgetting in the elderly individual has been suggested to mark the presence of a pathologic condition, such as Alzheimer's disease [97]. Specifying the nature of the memory deficits observed with changes in cortisol levels in aging could thus lead to highly sensitive markers of normal and pathological brain aging.

8. Conclusion

The primary aim of this review was to summarize and interpret data obtained in both animals and humans on the acute effects of corticosteroids on cognition and attempt to integrate them into a theoretical framework that could lead to future experiments. Our second aim was to critique the methodology used in the animal and human studies and to suggest new approaches for human cognitive research that would capitalize on findings and opportunities presented in animal research, and vice versa. We concentrated our review on the acute effects of corticosteroids on cognition and neither reported nor discussed data on stress-induced increases in corticosteroid levels. A closer look at this review, however, makes clear the need to discuss and separate these issues if one wants to make sense out of the large amount of data that has emerged in the past few years.

The review of data obtained in animals and humans on the acute effects of corticosteroids on cognition has led us to conclude that Type I and Type II receptors subserve different cognitive processes that are, however, closely linked to each other in time. According to our hypothesis, blockade or deficiency of Type I receptors would lead to an impairment in the basic functions of selective attention and sensory integration, thus making it more difficult for an individual to discriminate relevant cues from irrelevant ones. This would adversely affect the process of acquisition of memory, and impact other downstream aspects of memory, including consolidation and retrieval. With such a disturbance, an individual would show global deficits in learning and memory. In contrast, a deficiency or blockade of Type II receptors would leave the processes of sensory integration and selective attention untouched, while affecting consolidation and retrieval. With such a disturbance, an individual could still learn some new information and retain past experiences over a limited time, but would be very susceptible to forgetting and interference by other information.

It is tempting to relate the time-dependent effects of corticosteroids on cognitive function to the effects of Type I and Type II receptor activation on LTP in the hippocampus, and more particularly, on the induction of LTD after Type II steroid receptor activation. Because these effects have been produced with selective agonists for each receptor type, they may reflect the extreme end of receptor occupancy on cognitive function, particularly for Type II receptors. For Type I receptors, endogenous corticosteroids never occupy Type I receptors without occupying Type II receptors to some extent. Thus, a different effect of receptor activation may be observed in the moderate range of endogenous corticosteroid concentrations, resulting from occupation of Type I receptors and gradually increasing occupation of Type II receptors at the same time [85–87]. Indeed, the inverted-U shape relationship observed between corticosteroid concentrations and LTP in the hippocampus [54] suggests that moderate occupancy of Type II steroid receptor has positive effects on this physiological form of memory, while it is the high end occupancy of Type II steroid receptor with higher levels of corticosteroids that induce the negative effects (decrease in LTP, and induction of LTD) on these physiological models relevant to memory.

In conclusion, these results indicate that there are rapid and reversible acute effects of corticosteroids on cognition, meaning that stress-induced and diurnal variations of corticosteroids can affect cognition at different moments of an individual's life. Further studies on the time-course of corticosteroid actions on cognitive functions will thus be necessary in order to specify the nature and extent of cognitive deficits induced by corticosteroids in both animals and humans.

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