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MODULATION BY ADRENAL STEROIDS OF LIMBIC FUNCTION

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Summary—The effects of various steroid hormones on the long-term potentiation (LTP) of the rat hippocampus were evaluated. LTP was elicited in the dentate gyrus of adrenalectomized animals with priming tetanic stimulation (200 Hz–0.03 cps) of its main afferent, the perforant pathway. Single pulse EPSP (excitatory post-synaptic potential) slope, and PS (population spike) amplitude values were compared before and after the i.v. injection of the hormones and subsequently after the priming stimulation every 15 min up to 1 h. 18-OH-deoxycorticosterone (18-OH-DOC) produced a significant decrease of the EPSP LTP and arrested the PS enhancement in comparison with vehicle at every time post-tetanic stimulation. Its 21-acetate derivative produced a moderate decrease of the EPSP and had no effect on the PS LTP in comparison with vehicle. Deoxycorticosterone (DOC) exhibited similar effects on the EPSP although less marked than with 18-OH-DOC while the PS only decreased in the first 30 min post-train. Corticosterone decreased both EPSP and PS for the first 15 and 30 min after priming stimulation, respectively, matching values with those of vehicle afterwards. Its 21-acetate produced an initial decrease of the EPSP and had no effect on the PS LTP. Allo-tetrahydro-DOC produced little, if any, initial enhancement of the PS LTP in comparison with vehicle. These results show that the adrenal steroids tested can modulate hippocampal LTP, a plastic phenomenon in the mammalian CNS which is known to be related to memory and learning processes. Moreover, adrenal steroids can independently modify the PS or EPSP components of the LTP, suggesting different loci of action at the neuronal level.

INTRODUCTION

Changes during the evolutionary process have consisted largely in the development of specialized systems of control by codes of signals involving feedback, which allows more stable adjustments to the various phases of life [1]. Thus it is possible in endocrinology to recognize that new control systems and their extracellular messengers did not simply arise on demand. They evolved from what was already present by a process of gradual change [2–4].

Although earlier investigation of each hormone often seemed to indicate that it exerts only one specific action upon some part or tissue of the body, further studies have shown that in nearly every case the secreted substance influences not only specific distant cells but also some special aspect of the functioning of many cells throughout the body. For example secretion of the thyroid stimulates the respiration of many tissues in mammals, but not in fish, in which its action may be primarily on osmoregulation, and secondarily on metabolism. Similarly, insulin in the toadfish is concerned mainly with the metabolism of amino acids, in the cow with the metabolism of short-chain fatty acids, and in man with the metabolism of glucose [5].

When taken together, the information from various sources on the effects of hormones on body tissues, overwhelmingly supports Medawar's notion that "endocrine evolution is not an evolution of hormones but an evolution of the uses to which they are put; an evolution not, to put it crudely, of chemical formulae but of reactivities, reaction patterns and tissue competences" [6]. It therefore should not be surprising that, as is the case, nervous systems are important target sites for hormonal action. Behavioural and clinical work reveal that these effects may have important consequences. Thus

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frequent manifestations of Cushing's disease are affective disorders mostly in the form of depression [7–9]. In turn a significantly large population of patients, 44% with major depression and 50% with melancholia, show signs of adrenal hyperactivity with non-suppression in the dexamethasone suppression test [10]. As both of the clinical conditions mentioned, Cushing's disease and depression, show characteristic memory impairments, we thought it important to study at the experimental level the effects of adrenal steroids on the hippocampus of the rat. The hippocampus is a crucial structure in memory functions and both clinical and experimental data indicate that adrenal steroids can significantly affect these functions [11–14].

In the early 1970's, a long-term potentiation (LTP) of a synaptic transmission at a monosynaptic junction in mammalian hippocampus, a phenomenon that can last from hours to weeks, was described [15, 16]. The duration of the process, and the fact that it can be most easily elicited by using a priming stimulation sequence similar to naturally occurring neural bursts [17] led to the speculation that these electrophysiological changes could underlie memory and learning functions in the nervous system [15].

It is by now well established that the corticosteroid–hippocampal interaction is involved in the regulation of feedback mechanisms of adrenal steroid secretion [18]. Moreover, a great deal of the behavioural effects induced by glucocorticoid administration appear to be mediated by the hippocampal formation, the main CNS target for these hormones [18, 19].

For these reasons we thought it most appropriate to study the effects of adrenal steroids on a long-term phenomenon of the hippocampus (LTP) which would represent a model for memory and learning.

The results of these experiments may provide some answers as to how adrenal steroid hormones could affect behaviour.

MATERIALS AND METHODS

Sprague–Dawley male rats between 250–275 g (Charles River, Saint Hyacinthe, Quebec) were adrenalectomized via retroperitoneum under pentobarbital anesthesia (60 mg/kg i.p.) 48 h before recording. The animals were housed under standard light conditions (lights on from 5:00 to 19:00 h) and maintained on Purina chow and saline solution 0.9% *ad libitum*. All experiments were performed in the early afternoon to avoid the effects of circadian rhythm on LTP known to be modulated by adrenal cortex hormones [20]. Rats were anesthetized with chloral hydrate (0.4 gm/kg i.p.) for recording. The femoral artery and vein were cannulated for blood pressure recording and infusion of the hormones or vehicle, respectively. Rectal temperature was monitored by a thermic transducer connected to a feedback Y.S.I. (Yellow Springs Instrument Co. Inc., OH) system which maintained body temperature at 37°C by a d.c. heating pad.

Rats were placed in a conventional stereotaxic frame and a glass micropipette filled with NaCl 3M (2–5 mΩ impedance) was positioned at the level of the dentate gyrus (DG) for recording (coordinates: −3.5 mm from bregma, 1.9 mm lateral). Penetration of the pipette was guided by the audiovisual signal of the neuronal discharges from the granular cell layer of the DG, 5.8–6.0 mm above the interaural line. A bipolar stimulation electrode was lowered to the area of the perforant pathway (8.5 mm posterior to bregma, 3.8 mm lateral). The optimal excitatory post-synaptic potential (EPSP) response was obtained by adjusting the height of either the recording or stimulating electrodes. Verification of electrode position was performed by making anodal lesions with the stimulating electrode and by breaking the glass pipette and leaving it *in situ* for later histological examination.

Field potentials were amplified via a miniprobe (Stoelting PAD2A probe control) followed by a 2A61 Tektronik amplifier (bandwidth 6 Hz to 6 kHz) and then displayed on a Tektronik 565 oscilloscope. The output of this oscilloscope was fed into a Tektronik storage oscilloscope which served as a slave from which pictures were taken at the different stages of the experiments.

The slope of the EPSP was measured at a fixed time of 1 ms after the beginning of the initial positive deflection. The population spike (PS) amplitude was measured between the negative peak and a tangent line touching the two positive shoulders of the potential (Fig. 1).

1 mg of hormone was dissolved in 1 ml of Nutralipid (Pharmacia, Canada Inc.) 10% and injected in separate groups of rats ($n = 10$ per hormone). The effect of each hormone was compared with control rats ($n = 10$ per hormone) injected with the vehicle alone.

The steroids tested were: 18-hydroxy-deoxycorticosterone (18-OH-DOC) and 18-OH-DOC-21-acetate, which were donated by Dr Biollaz, (Ciba-Geigy, Basel); corticosterone (B); cortico-

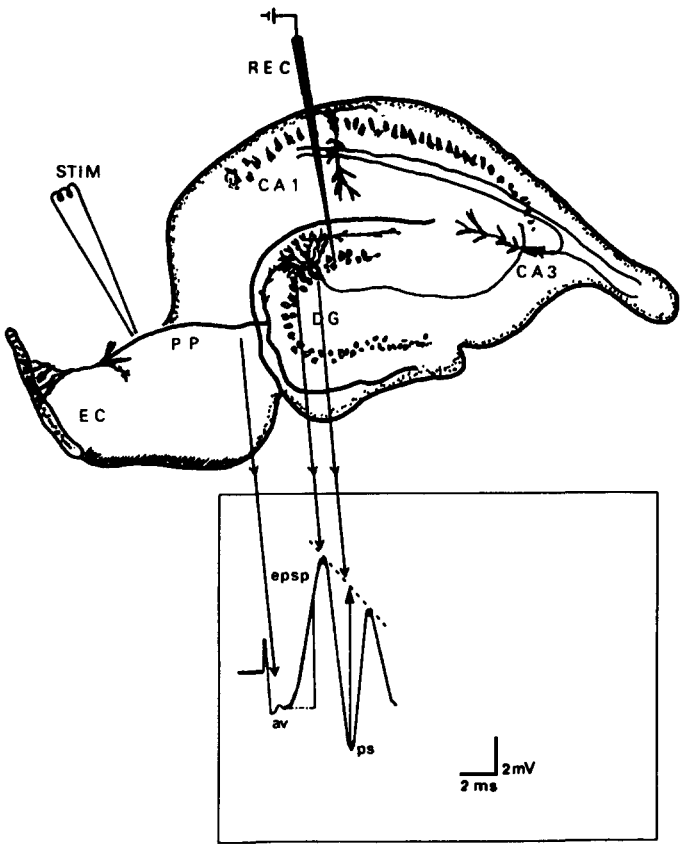

Fig. 1. Diagram depicting the position of the recording (REC) and stimulating (STIM) electrodes at the level of the DG and PP, respectively. Inset: typical evoked response recorded from the DG showing the afferent volley (av), the EPSP with the superimposed PS.

sterone-21-acetate (B-acetate); deoxycorticosterone (DOC) and allotetrahydrodeoxycorticosterone (allo-THDOC) these were purchased from Sigma (St Louis, MO).

Basal (pre-injection) and post-injection values of the EPSP and the PS components were obtained after a test pulse of 50 μs delivered to the perforant pathway (PP) with the pulse intensity

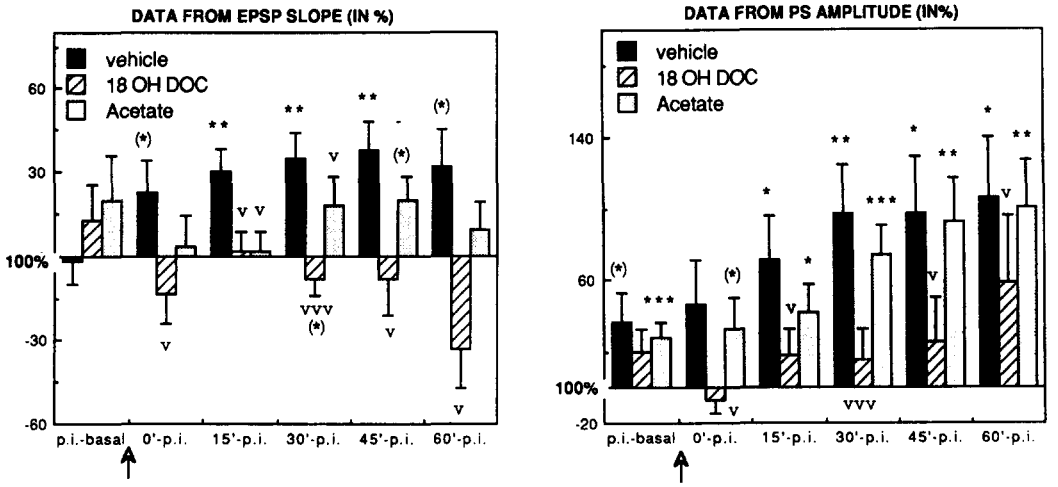

Fig. 2. Graph showing the relative percentage changes observed in the EPSP slopes (left panel) and PS amplitudes (right panel) obtained after the injection of vehicle, 18-OH-DOC and 18-OH-DOC-acetate (acetate). The arrow indicates the time of priming tetanic stimulation. Percentage changes of the EPSP and PS are compared against post-injection values (p.i.). Baseline is 100%. * Denote intrinsic statistical significance, ^{v} indicates significant vs vehicle. $^{*}P < 0.1$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; $^{v}P < 0.05$, $^{vvv}P < 0.001$ (two-tailed paired t-test).

adjusted to a level corresponding to 50% of the current required to produce a maximal response ($260 \pm 40\ \mu A$). The priming stimulation (200 Hz frequency trains of 1 s duration, at a rate of 0.03 Hz during 5 min) was given 2 min after the injection of the steroid or vehicle (rate: 0.5 ml/min). The EPSP and PS responses were evoked by a test pulse immediately following the priming tetanic stimulation and at 15 min intervals for the following hour.

RESULTS

The variations recorded in the EPSP amplitudes for 18-OH-DOC, acetate and vehicle are summarized in Fig. 2. The animals injected with vehicle showed significant enhancement of the EPSP slope at all times tested after the priming stimulation. By contrast, rats injected with 18-OH-DOC showed a depression of the EPSP at all times after priming stimulation that was maximally significantly different at 30 min when compared with the potentiation observed at that time in controls injected with the vehicle (difference between vehicle and 18-OH-DOC, $P < 0.001$). The EPSP response after priming in acetate-injected rats appeared intermediate to that observed with vehicle and 18-OH-DOC. Thus, the significant increase obtained with vehicle at 15 and 30 min after priming ($P < 0.01$) was not found with acetate (acetate vs vehicle $P < 0.05$), but at 45 min, acetate-treated animals displayed an increase of the EPSP of marginal significance ($P < 0.1$) and at both 30 and 45 min the EPSP values were significantly higher than those obtained with the parent hormone (difference between acetate and 18-OH-DOC, $P < 0.01$ and $P < 0.05$, respectively). There were no significant differences between pre- and post-injection values in either vehicle, 18-OH-DOC, or acetate-treated rats.

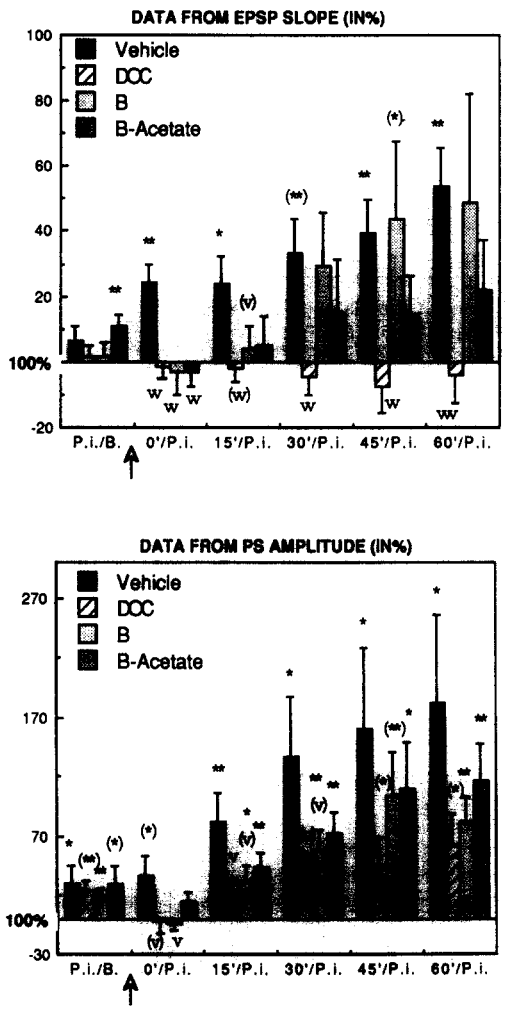

Fig. 3. Graph shows EPSP slope changes (upper panel) and PS amplitude values (lower panel) expressed in percentages after the injection of vehicle, DOC, B and B-acetate. Post injection (p.i.) values are compared against basal values (b). After priming tetanic stimulation (arrow) all values are compared against p.i. data. * Denote intrinsic significance: $*P < 0.1$, $*P < 0.05$, $**P < 0.02$, $**P < 0.01$ and ^{v}vs vehicle. $^{v}P < 0.1$, $^{vv}P < 0.02$, $^{vv}P < 0.01$, $^{vvv}P < 0.001$.

Figure 3 shows the effects on the EPSP of B-, B-acetate- and DOC-injected vs control rats. Again significant potentiation of the EPSP was present in vehicle controls at all times tested after priming stimulation. DOC injection produced a depression of the response at all times after priming stimulation, maximally significant at 1 h when compared with vehicle ($P < 0.001$). The effect of B consisted of a significant depression of the EPSP at 0 and 15 min when compared with vehicle ($P < 0.01$ and $P < 0.1$), then values paralleled those of control rats. With the injection of B-acetate a depression of the EPSP was observed at 0 min (vs vehicle $P < 0.01$) and then there was no difference in comparison to control rats. Comparison between basal and post-injection values of the EPSP was not significantly different for any of the groups when percentages were analysed, although when comparing the absolute values enhancement of marginal significance was found ($P < 0.1$) only with corticosterone-21-acetate (data not shown).

Effects on the PS component

With vehicle-injected rats the potentiation of the PS was significant starting at 15 min. Values obtained with 18-OH-DOC acetate showed no significant differences from controls and the intrinsic increment of the PS was significant at all times tested after priming stimulation.

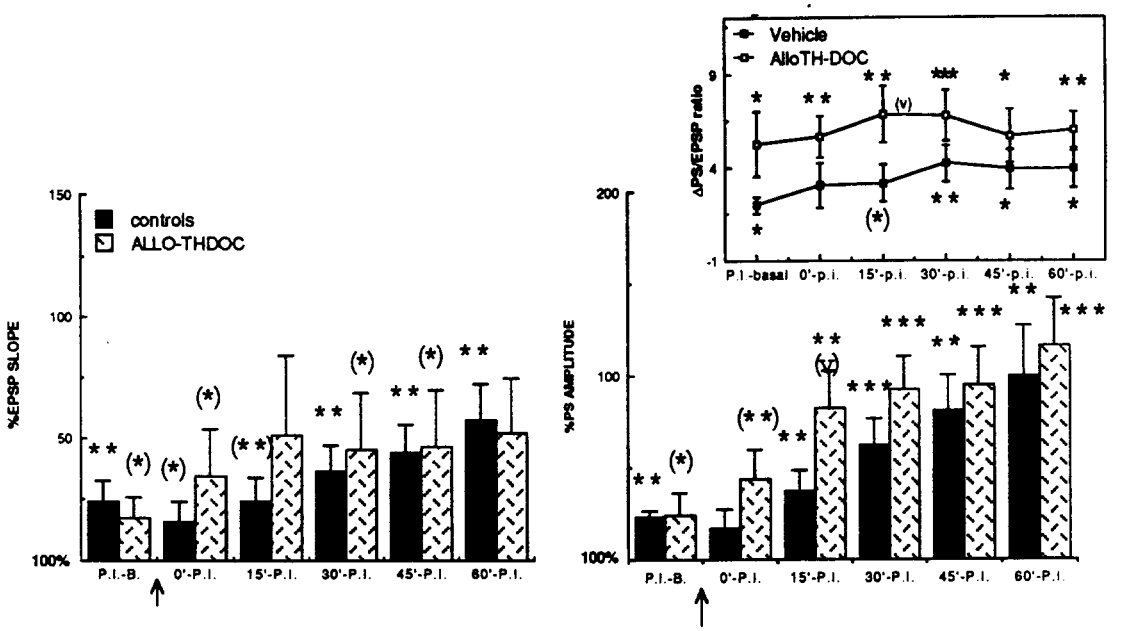

Fig. 4. Graph shows EPSP slope (left panel) and PS amplitude values (right panel) expressed in percentages after injection of allo-THDOC. Inset shows the variation of the ΔPS/EPSP ratio obtained from animals injected with allo-THDOC plotted against time. For statistical significance see legend to Fig. 3.

In comparison with vehicle, statistically significant decreases in the PS were elicited in the animals injected with 18-OH-DOC at all times after priming stimulation and maximally at 30 min as was the case for the EPSP (see Fig. 2).

Basal and post-injection PS values did not differ significantly in vehicle and 18-OH-DOC-injected animals, but the absolute as well as the percentage increase in PS obtained after injection with 18-OH-DOC acetate was statistically significant ($P < 0.05$ and $P < 0.001$, respectively). In the second series of experiments (Fig. 3) vehicle-injected rats also showed significant enhancement of the PS at all times after priming stimulation reaching an average increment of 180% over basal values when measured after 1 h. DOC produced an arrest of the PS LTP during the first 30 min which was maximally significant against vehicle at 15 min ($P < 0.05$). Subsequently values were below those of vehicle but not significantly different although an intrinsic increment of marginal significance was observed ($P < 0.1$ at 45 and 60 min). B produced lower values in the PS LTP than those of vehicle, maximally significant at 0 min ($P < 0.05$) and of marginal significance at 15 and 30 min ($P < 0.1$); an intrinsic increment of the PS LTP was observed after 15 min up to 1 h. B-acetate showed no significant difference in the PS values at any time in comparison with vehicle and significant intrinsic increments of the PS were obtained after 15 min and lasting up to 1 h. Post-injection vs basal values were found to be increased in the 4 groups of rats. Experiments performed with allo-THDOC (Fig. 4), known to be a potent anesthetic steroid [21], showed no significant difference in the development of EPSP LTP in comparison with controls. Similar results were observed in the PS although an increment over controls of marginal significance was observed at 15 min ($P < 0.1$).

Available data, see review in [16], supports the contention that the early portion of the monosynaptically evoked field potential is due to the extracellular current generated by the population of synchronously activated synapses and represents the extracellular equivalent of the intracellular EPSP. In turn, the later superimposed PS reflects the synchronous discharge of the population of target neurons, and hence involves the axon hillock of the neurons. Furthermore, it is well established that these two parameters, EPSP and PS, may be affected differently in LTP [15, 16].

We thought that as they represent different aspects of neuronal activity, a comparison of the ratios in time between the EPSP's and PS's between hormones and vehicle, can provide some information as to what aspect of neuronal activity, synaptic response or triggering of action potentials, could be more consistently affected by the hormones.

In the analysis of the ΔPS/EPSP ratio allo-THDOC (Fig. 4 inset) showed no significant

difference from controls except for an increase at 15 min post-train ($P < 0.1$) and an intrinsic significant increase in the spike–EPSP relation with time.

DISCUSSION

The data reveal that some adrenal pregnanes and their ring A-reduced metabolites significantly affect the development of a long-term phenomenon in the CNS, LTP.

Previous work [23–28] has documented that steroid hormones can induce rapid changes in neuronal behaviour in specific brain regions. These changes have been attributed to steroidal membrane effects [29, 30]. Their mediating mechanisms are debatable [26, 29], although binding sites have been described for steroid hormones in neural membranes [31], no specific steroid receptor has as yet been isolated.

The recent discovery that some steroidal components interact with the GABA receptor site in an agonistic way [32–34] while others, e.g. pregnenolone sulfate, inhibit the Cl channel [35], provided new insights into the steroid neuronal interaction. In fact the well-known anesthetic effects of some steroids has been attributed to this GABAergic effect [21, 22]. A strict structure–function relationship and dose dependence has been described for this effect. Both 5α and 5β pregnanes can produce this response. Essential features of the steroid structure appear to be a 3α hydroxyl group and a ketone group at position C20, the latter being necessary for high potency but not essential for activity [21]. 3β-OH derivatives are inert in this respect [22].

These structural characteristics do not appear to correspond with those required for steroids to affect LTP.

Thus, although with distinctive strengths, all three steroids, DOC, 18-OH-DOC and its acetate form, 18-OH-DOC-21-acetate, impair the development of LTP. In contrast a ring A-reduced metabolite of DOC, allo-THDOC, did not impair LTP development. However, at the dose used, 1 mg per rat, other effects could have occurred in the hippocampal formation. GABA can block LTP induction [32] and jointly with 3-α-OH-5-α-pregnane-20-one, THDOC, is one of the two steroid metabolites that most enhance GABA responses [22, 33]. Some of the excitatory (i.e. disinhibitory) effects of GABA on hippocampal neurons can be due to inhibition of GABAergic interneurons by GABAergic terminals [35]. Allo-THDOC can enhance the synaptic contacts on GABAergic interneurons, and in this way increase amplitude of hippocampal responses during LTP.

Both corticosterone and its 5α reduced metabolite 5α-DHB depressed development of LTP albeit in a different manner. B showed a clear biphasic effect on LTP, a significant decrease of the EPSP for 15 min and of the PS for 30 min immediately after the priming stimulation, and no significant differences from controls thereafter. On the other hand, 5α-DHB decreased PS values at all times after the priming stimulation and did not impair the EPSP [37]. It is of interest to note that the timing of these effects overlap with the time course of the two components of the LTP, as recently described by Davies *et al.* [38]. According to these authors, both pre- and post-synaptic mechanisms contribute to the maintenance of the LTP, but in a temporally distinct manner. Post-synaptic sensitivity changes could not be detected for at least 15 min after induction and took 2 h to reach maximum development in LTP. This implicates pre-synaptic mechanisms in the early stages of LTP. Within this context it can be recalled that steroids can act at pre-synaptic sites [34], and that 5α reductase, the rate-limiting enzyme for steroid metabolism, is found in larger amounts in white than in grey matter [39]. It is conceivable, then, that adrenal steroids can affect both early and late components of LTP, corresponding to the pre- and post-synaptic mechanisms of the phenomenon.

Considering that some of the steroid compounds could act through the Cl–GABA channel [21, 22, 35], our data suggest that other mechanisms may play a role in CNS–steroid interaction, as well as the known cytosol–receptor one.

That the results do not depend exclusively on an effect-related to the combination of the steroids with lipids on the cell wall is revealed by the results with 18-OH-DOC-21-acetate. This compound has an enhanced lipophilicity imparted by masking the 21 hydroxyl group. This notwithstanding, its effects on LTP were negligible compared with 18-OH-DOC itself.

The time course of the initiation of the phenomenon (*ca* 4 min after injection) makes mechanisms involving gene transduction unlikely.

The CNS is richly endowed with enzymes that metabolize steroid hormones 5-α-reductase and 3-ol-dehydrogenase [40]. Thus the possibility exists that all injected hormones act via the reduced metabolites. However, the significant

differences between the effects of parent compounds B and DOC, and their ring A-reduced metabolites, on LTP make this mode of action for B and DOC unlikely.

Additional mechanisms to explain the effects produced by steroid hormones on hippocampal LTP might be of relevance. Recent studies have shown that protein kinase C (PKC) is crucially involved in LTP development [41, 42]. Thus, factors influencing the molecular behavior of PKC could potentially affect the LTP. PKC could be a second messenger in associative learning and an increase in associated membrane PKC in hippocampal CA1 (regio superior) after conditioning training in rabbits has been reported [43]. Liu and Greengard [44] have demonstrated the presence of a tissue-specific cytosolic protein, whose extent of phosphorylation is regulated by both cAMP and steroid hormones. Studies suggest that this protein called SCARP, for steroid-cAMP-regulated-phosphoprotein, may be the regulatory subunit of the PKC [44]. Thus, if this is the case for hippocampal tissue, regulation of the level of phosphorylation of this protein can affect PKC and hence LTP development.

Other actions of glucocorticoid hormones in the brain as well as in peripheral tissues include the modulation of norepinephrine (NE) stimulated cAMP levels [18]. It has been shown that iontophoretic application of NE in the hippocampus can induce LTP *per se* [45]. In addition, adrenalectomy plus central NE depletion produces an up-regulation of β adrenergic receptors in hippocampal neurons, an effect which is restored by corticosterone administration.

It has not escaped our attention that the physiological and behavioral effects described for these steroid hormones and their metabolites could underlie, when disturbed, serious psychopathology. Thus both Cushing's and depressive disease are characteristically accompanied by memory disturbances [13, 15]. We have suggested [26] that hyperactivity of the adrenal glands may be a factor maintaining the depressive syndrome by helping to set the mood which bias memory mechanisms so characteristically towards the displeasure spectrum found in these patients. Further, we have shown that while DOC and corticosterone affect both brain excitability and feedback regulatory mechanisms, their ring A-reduced metabolites only affect CNS excitability while the effects of excitatory and depressant steroids can in many instances counteract each other in the CNS [24, 26]. Coupled with the dissociation between the effects of the hormones and their metabolites, these fundamental notions can serve as a basis for physiological therapeutics in neuroendocrine and psychiatric disorders produced by endocrine imbalance. In fact promising lines of clinical research have emerged from studies of steroid–CNS interaction [10, 12, 13, 46]. As Dr B. Murphy reported [47], we have also seen improvements in depressive patients showing hypercortisolemia and treated with ketoconazole, a steroid synthesis inhibitor [26].

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