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REVIEW

CORTICOSTEROIDS ENHANCE CONVULSION SUSCEPTIBILITY VIA CENTRAL MINERALOCORTICOID RECEPTORS

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SUMMARY

Recently, interest in the roles of central nervous system mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) has increased. In vitro results have implicated MR in the enhancing effects of corticosteroids and GR in the suppressing effects of corticosteroids on hippocampal excitability. Although indirect evidence exists suggesting that opposing actions of central MR and GR occur in vivo, direct evidence from studies employing receptor agonists and antagonists is only beginning to emerge. Work in our laboratory suggests that increased corticosterone levels are associated with increased severity of ethanol, pentobarbital, and diazepam withdrawal. Further work with chemical convulsants suggests that MR mediate excitatory effects of corticosteroids on convulsion susceptibility. The circadian rhythm in convulsion susceptibility varies with the circadian rhythm of plasma corticosterone levels and MR binding. The types of convulsions affected by manipulations of MR activity are believed to be of limbic origin, suggesting that limbic convulsions may be alleviated by the use of specific MR antagonists. In addition, because MR are substantially bound at rest and maximally occupied during the circadian peak in corticosteroid levels and during stressor exposure, these receptors are implicated in the maintenance of and in changes in the arousal state of animals.

Keywords—Receptors; Corticosteroid; Corticosterone; Convulsions; Drug withdrawal; Mice; Review.

INTRODUCTION

Attempts to elucidate the mechanisms through which corticosteroids exert effects upon central nervous system excitability have made considerable progress since the discovery of two corticosteroid receptor populations in the brain. These receptors belong to the steroid receptor superfamily of intracellular receptors which, following steroid binding, translocate

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to the nucleus and alter gene transcription. In the brain, mineralocorticoid receptors (MR) are localized primarily in the hippocampus and septal region, whereas the distribution of glucocorticoid receptors (GR) is widespread (Reul & de Kloet, 1985). Corticosterone, the principal corticosteroid of rodents is bound by MR (0.5 nM) with a higher affinity than by GR (5 nM). Rat hippocampal MR are approximately 35–45% activated under basal conditions during the circadian trough in corticosterone levels (Spencer et al., 1990). There is virtually no available hippocampal MR during conditions of acute stress or when corticosterone levels are at their circadian peak (Spencer et al., 1993). In contrast, hippocampal GR are only 5–15% activated under basal conditions and 30–35% occupied when corticosterone levels are at their circadian peak (Meaney et al., 1988; Spencer et al., 1993). This activation of GR increased to 50–60% following restraint stress and exogenous corticosterone administration (Meaney et al., 1988).

Central MR are involved in the regulation of basal Adrenocorticotropic hormone (ACTH) secretion throughout the circadian cycle (Bradbury et al., 1994; Dallman et al., 1989). GR are involved in the regulation of basal ACTH secretion during the diurnal peak and are involved in the regulation of ACTH during stressor exposure (de Kloet & Reul, 1987; Ratka et al., 1989). Sites of this negative feedback appear to include the paraventricular nuclei (Bradbury et al., 1994), medial prefrontal cortex (Diorio et al., 1993), and hippocampus (Sapolsky et al., 1990). Thus, MR and GR effects on regulation of the hypothalamic–pituitary–adrenal axis are coordinated based on their corticosterone binding characteristics.

Both excitatory and inhibitory effects of corticosteroids on nervous system excitability have been reported. Mineralocorticoids and low concentrations of corticosterone tend to be excitatory (Avanzino et al., 1984; Dafny et al., 1973; Diamond et al., 1992; Feldman et al., 1961; Joëls & de Kloet, 1990; Rey et al., 1987), whereas glucocorticoids and high concentrations of corticosterone tend to be inhibitory (Diamond et al., 1992; Joëls & de Kloet, 1989; Pfaff et al., 1971; Rey et al., 1989; Ruf & Steiner, 1967). For example, Diamond and colleagues (1992) showed increased primed burst potentiation in the hippocampus of anesthetized rats with plasma corticosterone concentrations of 11–20 μg/dl, whereas decreased primed burst potentiation was evident when plasma corticosterone levels were greater than 25 μg/dl. Based on the characteristics of the two types of corticosteroid receptors, it has been hypothesized that central MR mediate excitatory and central GR mediate inhibitory effects of corticosteroids on central nervous system excitability. However, even at relatively low circulating corticosterone concentrations, GR activation occurs. In order to better test this hypothesis, Joëls & de Kloet (1992) have examined the effects of various MR and GR agonists and antagonists on hippocampal slice electrophysiology. For example, they showed that the MR antagonist spironolactone blocked the excitatory effect of low corticosterone concentrations and the GR antagonist RU38486 blocked the inhibitory effect of higher corticosterone concentrations.

We have been interested in determining the potential role of MR in modulating central nervous system activity in the behaving animal. Therefore, we have examined the effects of corticosterone and the role of MR in mediating corticosteroid effects on central nervous system excitability in intact mice. This has been accomplished by investigating the effects of increasing and decreasing corticosterone levels on several convulsion types. These include handling-induced convulsions elicited following acute administration of the central nervous system depressants, ethanol, pentobarbital and diazepam, as well as convulsions produced by the chemical convulsants, pentylenetetrazol, kainic acid and strychnine. Although attempts were made to examine the effects of low corticosterone levels, in most cases levels

were well into the range of significant GR occupancy. Therefore, in order to more closely focus on MR actions, we have examined the effects of several receptor agonists and antagonists on susceptibility to chemically-induced convulsions.

CORTICOSTEROIDS AND DRUG WITHDRAWAL SEVERITY

Mice, genetically selected for severe convulsions during withdrawal from chronic ethanol exposure (Withdrawal Seizure Prone or WSP), were used in a series of experiments examining the effects of corticosterone on handling-induced convulsions following acute ethanol, pentobarbital and diazepam. Handling-induced convulsions are elicited by lifting the mouse by the tail and gently rolling the tail between the fingers so that the mouse rotates. This elicits mild tonic convulsions in drug-naive WSP mice and more severe tonic-clonic convulsions in drug withdrawing WSP mice. Convulsion signs are elicited in some mice simply by tail lift. Subcutaneous corticosterone pellets, resulting in plasma corticosterone levels of approximately 20 μg/dl, significantly increased handling-induced convulsion scores above those already elevated between 7 and 9 h following a single IP injection of 4 g/kg ethanol (Roberts et al., 1991). Acute administration of corticosterone also increased ethanol withdrawal severity (Fig. 1), while administration of the steroid synthesis inhibitor aminoglutethimide significantly decreased withdrawal severity in these mice. Withdrawal handling-induced convulsion scores of WSP mice following 60 mg/kg pentobarbital or 20 mg/kg diazepam (withdrawal precipitated with Ro15-1788) were also increased by acute corticosterone administration producing plasma corticosterone levels of approximately 20 μg/dl (Roberts et al., 1994; Fig. 1). This effect of corticosterone on drug withdrawal severity does not appear to be unique to WSP mice as ethanol withdrawal handling-induced convulsion scores of DBA/2J mice were also increased by elevations of corticosterone levels in the same range (Roberts et al., 1992).

There does, however, appear to be genetic variation in sensitivity to and release of corticosterone during ethanol withdrawal. Both naive and ethanol withdrawing Withdrawal Seizure Resistant (WSR) mice were insensitive to the excitatory effects of corticosterone on handling-induced convulsions (Roberts et al., 1991). WSR mice were selected for resistance to ethanol withdrawal and are almost void of any response after acute or chronic ethanol exposure. The corticosterone results suggest that the difference between WSP and WSR mice in severity of ethanol withdrawal may be due, in part, to a difference in sensitivity to the excitatory effects of corticosteroids. In other words, the increased sensitivity of WSP mice to corticosterone may result in the higher handling-induced convulsion scores observed in this mouse line. Another example of genetic variation in the role played by corticosterone in ethanol withdrawal severity comes from experiments with C57BL/6 and DBA/2 mice. C57BL/6 mice display lower plasma corticosterone levels during peak withdrawal and less severe withdrawal handling-induced convulsions than DBA/2 mice (Roberts et al., 1992), suggesting that genetic variability in corticosterone levels during withdrawal may influence the severity of withdrawal symptoms.

CORTICOSTEROID EFFECTS ON CHEMICALLY-INDUCED CONVULSIONS

Plasma corticosterone levels associated with increased withdrawal convulsion susceptibility are within the range associated with maximal MR binding, as well as considerable GR

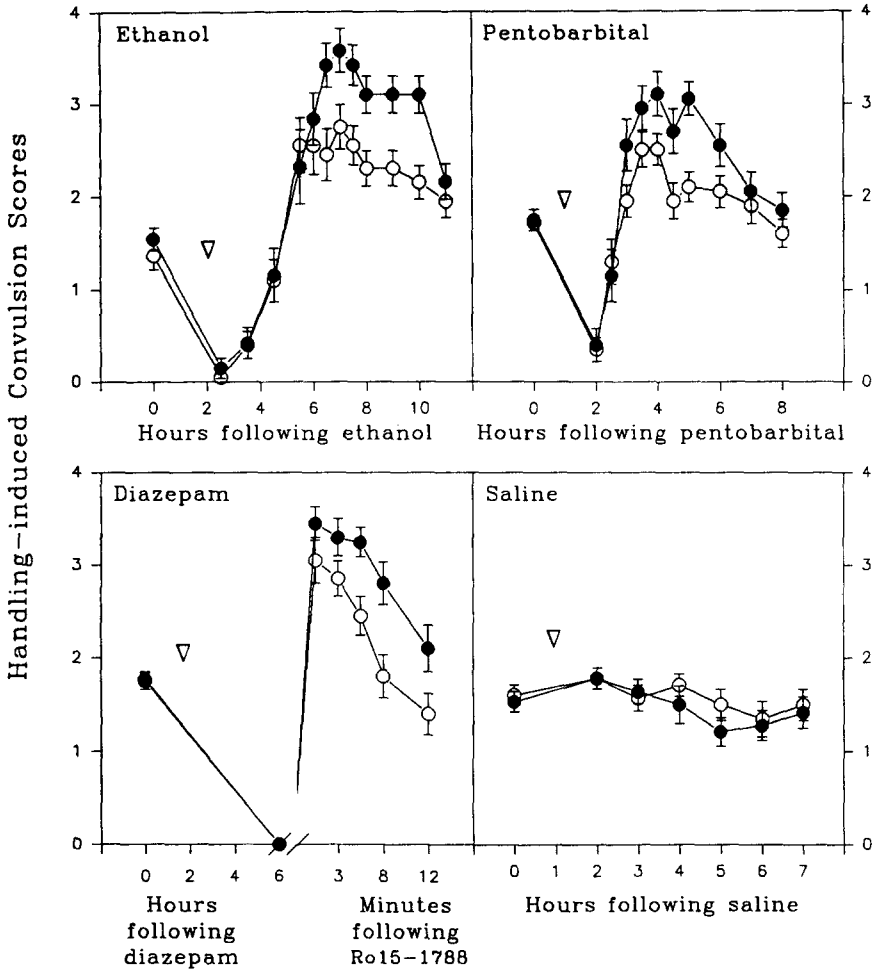

Fig. 1. Effects of corticosterone on central nervous system depressant withdrawal convulsions. Male WSP mice were injected IP with ethanol (4 g/kg), pentobarbital (60 mg/kg), diazepam (20 mg/kg; followed 6 h later by 10 mg/kg Ro15-1788), or saline. Corticosterone (20 mg/kg; filled circles) or the DMSO/sesame oil vehicle (open circles) was administered SC at the times indicated by inverted triangles. This dose of corticosterone resulted in plasma levels of 15–28 μg/dl (versus 4–6 μg/dl in vehicle-treated controls) at the time of peak withdrawal. Corticosterone significantly enhanced handling-induced convulsion scores above those already elevated following ethanol, pentobarbital, or diazepam. Corticosterone did not affect the decrease in handling-induced convulsions observed immediately following central nervous system depressant administration or handling-induced convulsions following saline administration. These results suggest that corticosterone exacerbates the severity of withdrawal convulsions from a variety of drugs of abuse. Reprinted with permission from Roberts AJ, Crabbe JC, Keith LD (1994) Corticosterone increases severity of acute withdrawal from ethanol, pentobarbital, and diazepam in mice. Psychopharmacology 115:278–284.

binding (Spencer et al., 1993). In order to more fully investigate the role of corticosteroids in mediating the proconvulsant effects of corticosterone, we have employed systemic administration of chemical convulsants. Chemical convulsants have been used to model various seizure types. For example, pentylenetetrazol (PTZ), which blocks chloride influx

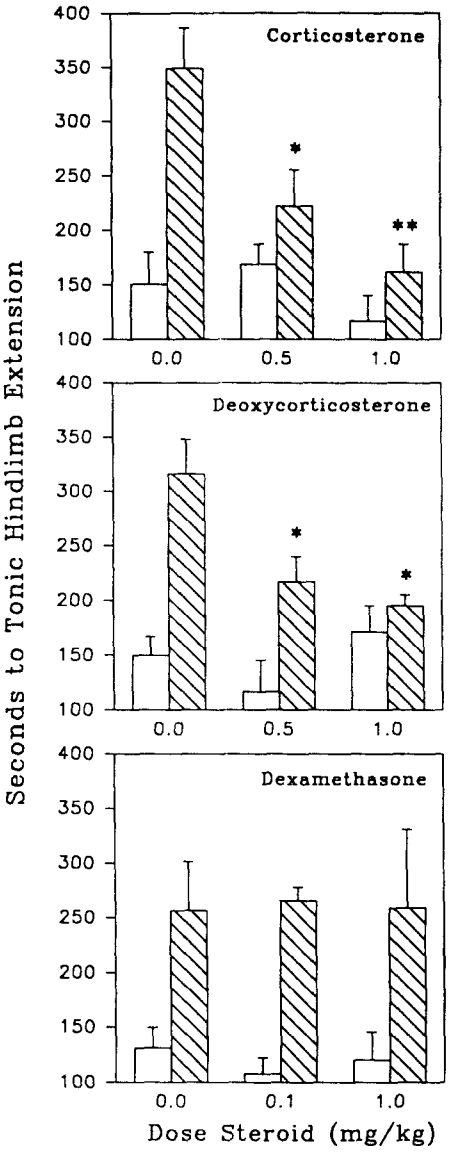

Fig. 2. Reversal of the anticonvulsant effect of aminoglutethimide by corticosterone and deoxycorticosterone, but not dexamethasone. Male WSP mice were injected SC with 25 mg/kg aminoglutethimide (hatched bars) or the DMSO/sesame oil vehicle (open bars). In the same injection, one of three steroids was replaced. These were 0, 0.5, or 1 mg/kg corticosterone, 0, 0.5, or 1 mg/kg deoxycorticosterone, or 0, 0.1, or 0.5 mg/kg dexamethasone. A lower intermediate dose of dexamethasone was chosen because this hormone is not bound by corticosterone-binding globulin and was therefore expected to be circulating at considerably higher free levels. One hour later, 145 mg/kg PTZ was administered IP and latencies to tonic hindlimb extension convulsions were recorded. Without replacement steroids, aminoglutethimide significantly increased latencies to PTZ-induced convulsions. However, corticosterone and deoxycorticosterone significantly reversed this effect ($^{*}p < .05$, $^{**}p < .01$, compared to the aminoglutethimide only group), while dexamethasone was ineffective. This suggests that steroids with pronounced mineralocorticoid but not glucocorticoid action can antagonize the anticonvulsant effect of aminoglutethimide. Furthermore, this implicates central MR mediating excitatory corticosteroid effects. Reprinted from Roberts AJ, Crabbe JC, Keith LD (1993) Type I corticosteroid receptors modulate PTZ-induced convulsions of withdrawal seizure-prone mice. Brain Res 626:143–148.

through $GABA_A$ receptor channels, is used to model generalized seizures and is widely used in anticonvulsant screening tests (Gale, 1988; Krall et al., 1978). Strychnine, which decreases chloride influx via its action as a glycine receptor antagonist, is used to model seizures of spinal cord and brainstem origin (Curtis et al., 1971; Fisher, 1989). Kainic acid (KA) increases cation conductances through its action as a glutamate agonist and is used to model complex partial (limbic) epilepsy (Patel, 1988).

The steroid synthesis inhibitor aminoglutethimide increased latencies to tonic hindlimb extension following IP administration of PTZ in WSP mice (Roberts et al., 1993a). Low, anticonvulsant doses of aminoglutethimide significantly decreased corticosterone levels, but had no general central nervous system depressant effect as indexed by measures of motor performance and body temperature (Roberts et al., 1993b). Corticosterone administration, producing plasma concentrations of approximately 16 μg/dl, was sufficient to reverse the anticonvulsant effects of aminoglutethimide. In addition, the MR agonist deoxycorticosterone, but not the GR agonist dexamethasone, reversed the effect of aminoglutethimide on PTZ-induced tonic hindlimb extension (Roberts et al., 1993a; Fig. 2). Furthermore, two MR antagonists, spironolactone and RU 26752, displayed a moderate anticonvulsant effect upon PTZ-induced convulsions (Roberts et al., 1993a). Collectively, these results suggest that MR activation is important in the maintenance of convulsion susceptibility.

WSP mice were used in much of this original work as these mice were shown to be sensitive to the excitatory effects of corticosterone on acute ethanol withdrawal convulsions. In order to rule out a potentially unique role of corticosteroids in these selectively bred mice, we extended the results of the above studies to mice with a heterogeneous genetic makeup. These mice were the product of an eight-way cross of genetically diverse inbred strains. In order to examine the neuroanatomical and/or neurochemical specificity of MR-mediated corticosteroid effects, convulsions elicited by IV kainic acid and strychnine, as well as PTZ, were utilized.

Excitatory effects of corticosterone and inhibitory effects of aminoglutethimide were observed in several instances (Roberts & Keith, 1994a). Doses of PTZ required for myoclonic jerk and face and forelimb clonus, and doses of KA required for wild running clonus and tonic hindlimb extension, were altered consistently by these manipulations. Unaffected convulsions included strychnine-induced myoclonic jerk, running bouncing clonus and tonic hindlimb extension, and PTZ-induced running bouncing clonus. The excitatory effects of corticosterone occurred when plasma levels were between 13 and 16 μg/dl, suggesting a role for MR in this effect. Indeed, these proconvulsant effects were blocked by the MR antagonist spironolactone (Fig. 3).

It was interesting that not all of the convulsion types investigated were affected by these MR manipulations. This suggests that corticosteroid effects are not global. MR may modulate GABAergic or excitatory amino acid neurotransmission, as these systems are likely to be the principle targets of PTZ and KA, respectively. However, corticosterone effects on excitatory amino acid neurotransmission appear to be primarily mediated via GR as corticosterone levels associated with stress quadrupled the increase in glutamate released following KA-induced seizures (Stein-Behrens et al., 1994). Nonetheless, there was a doubling of hippocampal glutamate released following KA seizures when corticosterone levels were increased from 0 to 10 μg/dl, which may represent a small MR effect (ibid).

The convulsions found to be affected by MR manipulations are believed to originate in limbic structures (Gale, 1988; Magistris et al., 1988; Miller & Ferrendelli, 1988; Patel, 1988). In contrast, those convulsions found to be unaffected by manipulations are believed to

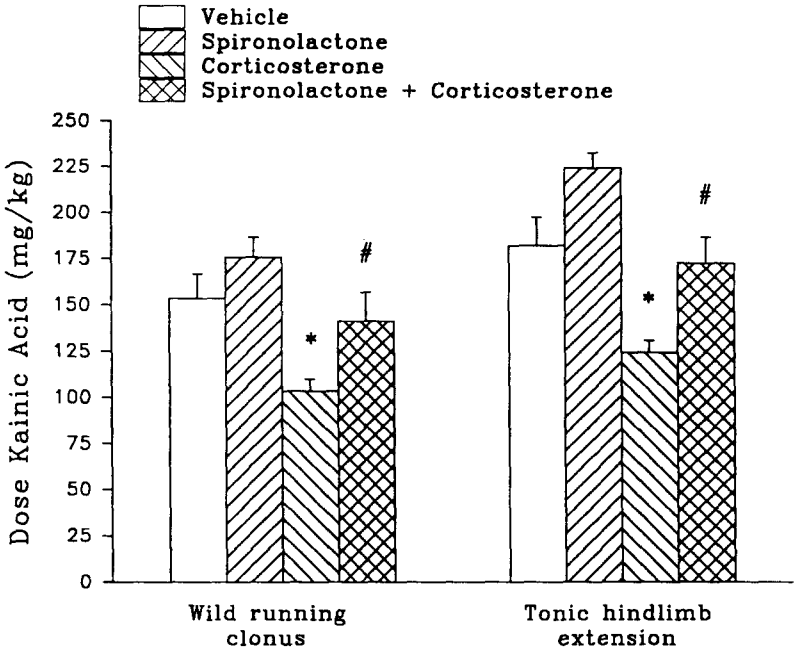

Fig. 3. The effect of corticosterone, spironolactone, or their co-administration on kainic acid-induced convulsions. Genetically heterogeneous male mice were injected SC with either the DMSO/sesame oil vehicle or 5 mg/kg spironolactone, each followed immediately by the vehicle or 1 mg/kg corticosterone. One hour later, 5 mg/ml kainic acid was infused into a lateral tail vein at a rate of 0.5 ml/min. Latencies to wild running clonus and tonic hindlimb extension were recorded and later converted to threshold doses. Corticosterone significantly decreased the dose of kainic acid required for both convulsions ($^{*}p < .05$, compared to the vehicle group). This proconvulsant effect of corticosterone was blocked by co-administration of spironolactone ($\#p < .05$, compared to the corticosterone group). These results suggest that the proconvulsant effect of corticosterone on kainic acid-induced convulsions is mediated via MR. Reprinted with permission from Roberts AJ, Keith LD (1994) Mineralocorticoid receptors mediate the enhancing effects of corticosterone on convulsion susceptibility in mice. J. Pharmacol Exp Ther 270:505–511.

originate in the brainstem or spinal cord (Franz, 1980; Magistris et al., 1988; Miller & Ferrendelli, 1988). An intriguing target for MR action in the hippocampus which is likely to alter excitability is the Na^+–K^+–ATPase. It has recently been shown that the MR selective agonist aldosterone significantly increased the expression of the α_3-subunit of this enzyme in the dentate gyrus and CA1 and CA4 hippocampal neurons (Farman et al., 1994). There was no effect in parietal cortex neurons or in glia and very different effects in peripheral tissues, suggesting cell and regional specificity of actions. Future experiments are needed to determine whether MR-induced changes in Na^+–K^+–ATPase activity result in a significant alteration in neuronal excitability.

If MR binding affects susceptibility to convulsions of limbic origin, it would be expected that susceptibility to KA-induced convulsions would vary with the circadian rhythm in MR binding. In nocturnal rodents, corticosterone levels and MR binding are at their lowest in the morning and rise around the time of lights off when the animal begins its active period. In fact, we found that susceptibility to KA-induced convulsions displayed a circadian rhythm

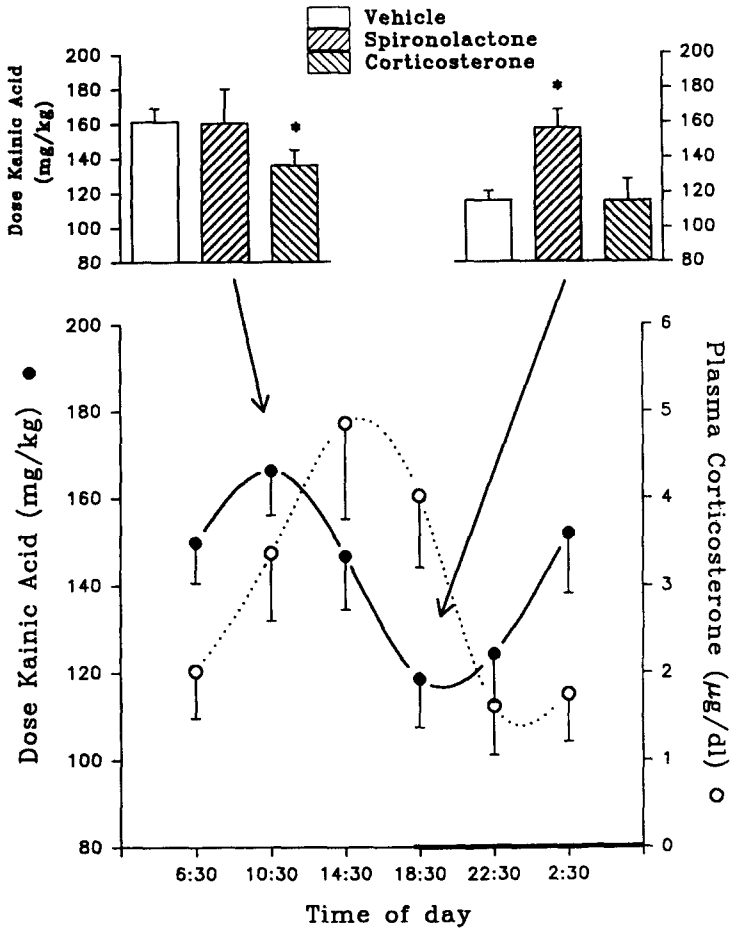

Fig. 4. Circadian variation in kainic acid-induced wild running clonus and plasma corticosterone levels (bottom panel) and the effects of corticosterone and spironolactone at the times of least (top left panel) and greatest (top right panel) susceptibility. Male heterogeneous stock mice were used in these experiments. In the first experiment (bottom panel), mice were quietly and rapidly removed from their home cages and infused via a lateral tail vein with kainic acid (5 mg/ml at a rate of 0.5 ml/min). Latencies to wild running clonus were recorded and later converted to threshold doses. Blood was immediately sampled for plasma corticosterone determinations. The dark line on the abscissa denotes the period of lights off in the home room. There was a clear circadian rhythm in susceptibility to kainic acid-induced convulsions (solid line), with higher doses required in the morning (rodents' inactive time) and lower doses required in the evening (rodents' active time). Plasma corticosterone levels also displayed circadian rhythmicity (dotted line), with the highest levels in the evening and the lowest levels in the late night and early morning. In the next experiment (top panels), mice were injected SC with the DMSO/sesame oil vehicle, 1 mg/kg corticosterone, or 5 mg/kg spironolactone in the morning or the evening. One hour later (at 1030h or 1830h) mice were infused with kainic acid. Corticosterone significantly decreased the dose of kainic acid required to induce wild running clonus in the morning ($^{*}p < .05$), whereas spironolactone had no effect at this time. In contrast, corticosterone had no effect in the evening, whereas spironolactone significantly increased the dose of kainic acid required to induce wild running clonus ($^{*}p < .05$). These differential effects of corticosterone and spironolactone at times when MR occupancies are different suggest that the degree of MR occupancy plays a role in the sensitivity of these animals to kainic acid-induced convulsions. Reprinted with permission from Roberts AJ, Keith LD (1994) Sensitivity of the arcadian rhythm of kainic acid induced convulsion susceptibility to manipulations of corticosterone levels and mineralocorticoid receptor binding. Neuropharmacology 33:1087–1093.

with greatest susceptibility in the evening and least susceptibility in the morning (Roberts & Keith, 1994b). Times of putatively greater MR binding were associated with greater convulsion susceptibility. The effects of corticosterone and spironolactone at the times of peak and trough susceptibility were examined. We predicted that the proconvulsant effect of corticosterone would be greatest in the morning when MR occupancy is submaximal, whereas the anticonvulsant effect of spironolactone would be expected to be greater in the evening when MR occupancy is maximal. The results confirmed this prediction (Fig. 4) and strengthen the hypothesis that MR mediate the excitatory effects of corticosterone on central nervous system excitability. In addition, they suggest that the circadian rhythm in susceptibility to KA-induced convulsions can be modulated by alterations in MR binding. A significant degree of GR occupation occurs with corticosterone levels at their circadian peak; however, as spironolactone completely blocked the circadian increase in convulsion susceptibility, it appears that MR action is more critical than GR action in circadian fluctuations in convulsion susceptibility.

SIGNIFICANCE OF CENTRAL MR EFFECTS

Taken together, the results of our experiments using chemical convulsants suggest that MR play a role in mediating convulsions of limbic origin. This suggests that the degree of MR occupancy may affect the frequency and/or severity of seizures in humans with partial complex (limbic) epilepsy. Indirect support for this suggestion comes from a report indicating that partial seizures in humans occur more frequently during the day time (Billiard, 1982; Poirel, 1991), when plasma cortisol levels are at their circadian maximum. Consistent with this, mice were more susceptible to KA-induced convulsions during their wakeful period, when plasma corticosterone levels were around their circadian maximum (Roberts & Keith, 1994a). In addition, a positive association was found between subjective stress and seizure frequency in adult epileptics (Lambie et al., 1986; Mattson, 1991; Temkin & Davis, 1984). Complex partial epilepsy tended to show a greater association between seizure frequency and stress than did generalized epilepsy (Stevens, 1958; Webster et al., 1988). This suggests that limbic seizures are uniquely sensitive to an individual's stress state. Therefore, MR antagonists may prove useful for treatment of complex partial epilepsy, which is the most difficult form of epilepsy to treat with currently available anticonvulsants (Fisher, 1989).

To date, the most compelling evidence for clinical application of central MR antagonism is in the treatment of complex partial epilepsy. However, a better understanding of the role of corticosteroids in drug withdrawal convulsion severity may lead to a more effective treatment of this syndrome. For example, drug withdrawal convulsions were affected by alterations in corticosteroid levels, suggesting that they are sensitive to the stress state of an animal. Further investigation of the coordinated actions of central MR and GR will provide a greater understanding of the role of stress in disease states involving the central nervous system.

The effects of MR action on central nervous system excitability undoubtedly extend past modulation of disease states. Evidence is accumulating which suggests that animals will self-administer corticosterone orally (Piazza et al., 1993) and intravenously (Deroche et al., 1993). In fact, preliminary studies have shown that several inbred strains of mice consume enough corticosterone (when presented with a choice between corticosterone-21-hemisuccinate in tap water and plain tap water) to produce significant elevations in

handling-induced convulsion scores (Roberts & Phillips, unpublished observation). This implies that mice will self-administer enough corticosterone to enhance nervous system excitability and suggests that this effect of corticosterone may possess reinforcing properties.

The excitatory effects of MR on central nervous system activity may serve to enhance arousal states of animals. Maximum MR occupancy in both nocturnal and diurnal animals occurs just prior to waking and, therefore, may aid the arousal process. In addition, mild stressor exposure at times when circadian corticosteroid levels are low would be expected to result in increased MR binding. In contrast, mild stressor exposure when circadian levels of corticosteroid are higher would not result in further increases in MR binding, but would be associated with significant activation of GR. The coordination of MR and GR actions may permit animals to cope with stressful situations at times of decreased arousal and ignore mildly stressful situations during wakefulness.

The concept of a role of MR in arousal is consistent with electrophysiological results supporting MR involvement in the maintenance of excitability in the nervous system (de Kloet et al., 1991; Joëls & de Kloet, 1992). This electrophysiological work suggests that MR activation maintains synaptic transmission from amino acid-carried Schaffer fibers in the CA1 area of the hippocampus (Joëls et al., 1994). In addition, serotonergic and cholinergic hyperpolarizations of CA1 neurons were decreased by the MR agonist aldosterone (ibid). The recent work of Farman et al. (1994) suggests that, perhaps, the enhancing effect of aldosterone on Na^+–K^+–ATPase activity may mediate the MR-induced enhancement of hippocampal excitability. In addition to electrophysiological findings, the effects of MR antagonists on behavior in a spatial learning task also support a role for this receptor in modulating the state of arousal of animals (Oitzl & de Kloet, 1992). GR activity is often found to possess effects which oppose those of MR on electrophysiological parameters, suggesting a coordinated response to corticosteroids, allowing for adaptation under situations of stress as well as under basal conditions throughout the circadian cycle. The work presented here suggests that MR effects on nervous system excitability can be detected in behaving animals and it supports in vitro electrophysiological results showing excitatory effects of MR.

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