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Acute rise in corticosterone facilitates 5-HT_{1A} receptor-mediated behavioural responses

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Abstract

Corticosterone influences 5-HT_{1A} receptor-mediated responses in the rat hippocampus in vitro: activation of the high affinity mineralocorticoid receptor suppresses 5-HT_{1A} receptor-mediated hyperpolarization, while subsequent activation of lower affinity glucocorticoid receptors enhances the effect of 5-HT. We have tested whether a similar effect of corticosterone exists in vivo. In intact rats, a systemic injection of the specific 5-HT_{1A} receptor agonist, 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin), led to increased locomotion and to a less persistent search strategy in the free swim trial of the Morris water maze test. Adrenalectomized rats with a corticosterone-pellet implanted as replacement received an injection of vehicle (predominant mineralocorticoid receptor occupation) or a high dose of corticosterone (both corticosteroid receptor types occupied) 1 h before injection of 8-OH-DPAT. The effect on search strategy, but not on locomotor activity, was less in animals with low corticosterone levels. The results suggest that hippocampal 5-HT_{1A} receptor-mediated responses in vivo are attenuated during predominant activation of the mineralocorticoid receptor and increased after additional transient activation of the glucocorticoid receptor.

Keywords: 5-HT_{1A} receptor; Mineralocorticoid receptor; Glucocorticoid receptor; Hippocampus; Corticosterone; Spatial learning

1. Introduction

The actions of corticosterone on the hippocampus are mediated by two types of corticosteroid receptors. The high-affinity mineralocorticoid receptor and the low affinity glucocorticoid receptor are co-localized in hippocampal neurons (Van Eekelen et al., 1988; Van Steensel et al., 1996). Mineralo- and glucocorticoid receptors are differentially occupied at different levels of circulating corticosterone. Around the circadian trough of corticosterone secretion, mineralocorticoid receptors are predominantly occupied; around the circadian peak and after stress, the output of the hypothalamic–pituitary–adrenal axis is increased and both corticosteroid receptor types are occupied by corticosterone (Reul et al., 1987; Spencer et al., 1993).

The 5-HT_{1A} receptor is very highly expressed in the CA1 pyramidal cells and dentate granular neurons of the hippocampus (Chalmers and Watson, 1991; Pompeiano et al., 1992). The CA1 pyramidal neurons show 5-HT_{1A} receptor-mediated hyperpolarization in response to 5-HT application (Andrade and Nicoll, 1987). In the hippocampal slice preparation, this response is suppressed by predominant occupation of mineralocorticoid receptors, e.g., after in vitro exposure to aldosterone (Joëls et al., 1991). Combined occupation of mineralo- and glucocorticoid receptors restores the responsiveness to 5-HT_{1A} receptor stimulation as becomes apparent after combined administration of aldosterone, a mineralocorticoid receptor agonist, and the glucocorticoid receptor agonist, RU28362 (11β,17β-dihydroxy-6-methyl-17α(1-propynyl)-androsta-1,4,6-trione-3-one), to the hippocampal slice (Joëls and De Kloet, 1992).

In the present experiments, we tested the hypothesis that a similar mechanism of action of corticosterone, involving both receptor types, operates in vivo in rats. We used the Morris water maze, a spatial learning and memory task, the execution of which depends on the integrity of the

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hippocampus (Morris et al., 1982). Administration of the specific 5-HT_{1A} receptor agonist, 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) (Arvidsson et al., 1981), interferes with the performance of rats in this task via activation of postsynaptic 5-HT_{1A} receptors in the hippocampus (Hunter and Roberts, 1988; Carli and Samanin, 1992; Carli et al., 1992). We studied the effect of differential corticosteroid receptor occupation on the responsiveness to 8-OH-DPAT in the free swim trial of the Morris maze task, when the behaviour of trained animals is monitored in the absence of an escape platform in the pool.

We tested the effect of 8-OH-DPAT both in intact rats, and in adrenalectomized rats with corticosterone replacement rats. As the effect of corticosterone on 5-HT_{1A} receptor responsiveness develops within an hour (Joëls and De Kloet, 1992), we looked for a design in which differential occupation of corticosteroid receptors could be obtained acutely before administration of 8-OH-DPAT. Because 8-OH-DPAT is a potent activator of the hypothalamic–pituitary–adrenal axis (Fuller, 1992), we used adrenalectomized rats subcutaneously implanted with a pellet containing 20 mg corticosterone. Injection of a high dose of corticosterone shortly before testing superimposed transient activation of both receptor types on the condition of constant predominant mineralocorticoid receptor occupancy maintained by low levels of corticosterone. We found that 5-HT_{1A} receptor-mediated response involving search strategy was specifically sensitive to variations in corticosterone occupation. These responses were low in animals with a predominant mineralocorticoid receptor occupation, but enhanced in rats that had both corticosteroid receptors occupied.

Part of these data was reported previously in abstract form (Meijer et al., 1994).

2. Materials and methods

2.1. Animals and surgery

Male Wistar rats, weighing 180–200 g at the time of surgery, were used. The animals were housed three per cage and had free access to food and water. Adrenalectomized rats had additional access to 0.9% saline. The rats were housed under a 12:12 h light–dark cycle, with lights on at 0700 h. All behavioural training took place between 0800 and 1400 h. The free swim trial (see below) took place between 0900 and 1200 h. Rats were sham-operated (experiment 1) or adrenalectomized (experiment 2) in the morning under ether anaesthesia using the dorsal approach. Adrenalectomized rats had a pellet containing 20 mg corticosterone (Sigma, St. Louis) and 80 mg cholesterol implanted subcutaneously in the neck to ensure constant low levels of corticosterone in the blood. All experiments were carried out in accordance with the European Communities Council Directive 86/609/EEC; all efforts were made to minimize animal suffering during the experiments. The protocols were approved by the Committee for Animal Care and Ethics of the Faculty of Medicine and Faculty of Natural Sciences, University of Leiden, Netherlands.

2.2. Drug treatment and experimental groups

Training and treatment schedules for the rats are depicted schematically in Fig. 1. Intact rats were subcutaneously injected with 8-OH-DPAT ((±)-8-hydroxy-2-(di-*n*-propylamino)-tetralin; 100 μg/kg or 300 μg/kg body weight; Sigma, St. Louis) or saline 30 min before the free swim trial, resulting in the following experimental groups: sham-saline ($n = 9$), sham-100 μg/kg 8-OH-DPAT ($n = 9$), sham-300 μg/kg 8-OH-DPAT ($n = 9$). Adrenalectomized/pellet-replacement animals were injected s.c. with 1 mg/kg corticosterone dissolved in polyethyleneglycol-300 ('High B') or the solvent only ('Low B') 60 min prior to injection of 8-OH-DPAT at 100 μg/kg or 300 μg/kg body weight. For the corticosterone replacement experiment, this led to the following six experimental groups: Low B-saline ($n = 9$), Low B-100 μg/kg 8-OH-DPAT ($n = 9$), Low B-300 μg/kg 8-OH-DPAT ($n = 10$), High B-saline ($n = 14$), High B-100 μg/kg 8-OH-DPAT ($n = 13$), and High B-300 μg/kg 8-OH-DPAT ($n = 10$).

2.3. Spatial navigation apparatus

The water maze was a circular pool (140 cm in diameter and 50 cm in height) filled with warm water (30 cm

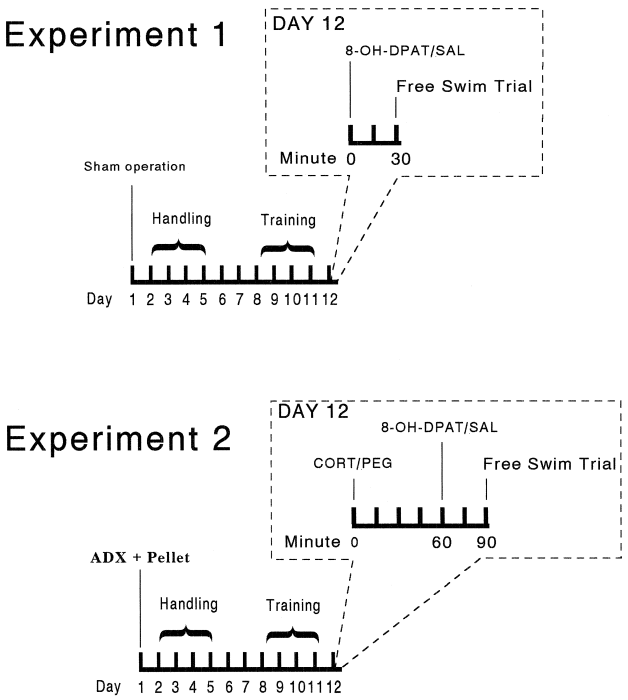

Fig. 1. Experimental design.

depth; 26 ± 1°C). An escape platform (11 cm diameter; 1.5 cm below the water surface) was located in a fixed position equidistant from the centre and the wall of the pool. The testing room contained numerous extra-maze cues. The behaviour of the rats was monitored with a video camera mounted above the centre of the pool. For data analysis, the pool was divided into four quadrants of equal size. Recording and analysis of data were performed with an image analysis program (Ethovision 1.70, Noldus Information Technology, Wageningen, Netherlands).

2.4. Acquisition of the escape task

The rats were trained for four days to learn the position of the escape platform. Acquisition of the escape task started one week after surgery. Four starting positions that were equally spaced around the pool were selected. Each of these starting positions was used once a day for each rat in a semi-random order, i.e., four learning trials took place per day for each rat. A trial started with placing of the animal in the water, facing the wall of the pool, at one of the starting positions. The latency to find the escape platform was recorded. If the animal did not locate the platform within 120 s, it was led there by the experimenter. The animals were left on the platform for at least 20 s. After the last trial, the animals were dried under a red-light heating lamp. The intertrial interval was 1 to 6 min.

2.5. Free swim trial

On the fifth day, the platform was removed from the water and one 'free swim trial' that lasted 60 s was given. The following parameters of the rats' search behaviour were monitored: (i) the distance swum until the first crossing of the former platform position. This reflects the memory for the location of the platform. (ii) The percentage of time spent in the quadrant of the pool where the platform was formerly located. The time the animals spent there reflects the persistence of the search. (iii) The number of crossings of the former platform position per metre swum. This parameter is normalized for the distance swum because the drug treatment increases swimming speed and thus, might affect the number of 'random' crossings of the former platform location. This parameter is also a measure of the acuity of the search. (iv) The total distance swum. 5-HT_{1A} receptor activation is known to increase locomotor activity. Thus, the efficiency of the drug can be validated by measuring this parameter.

The animals were decapitated within 2 min after the free swim trial. Trunk blood was collected in EDTA-coated tubes to determine plasma corticosterone levels. The brains

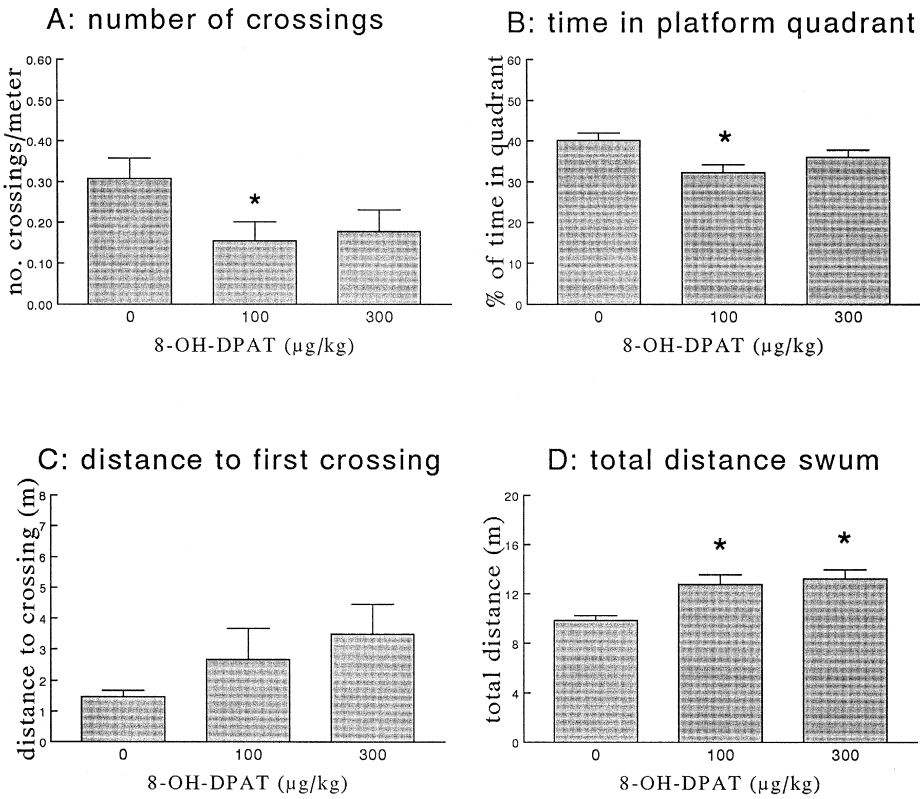

Fig. 2. Performance of intact rats in the free swim trial of the water maze, 30 min after injection of 8-OH-DPAT. (A) and (B) depict persistence in search behaviour; immediate recall of the platform position is presented in (C) and effects on locomotor behaviour in (D). $* P < 0.05$.

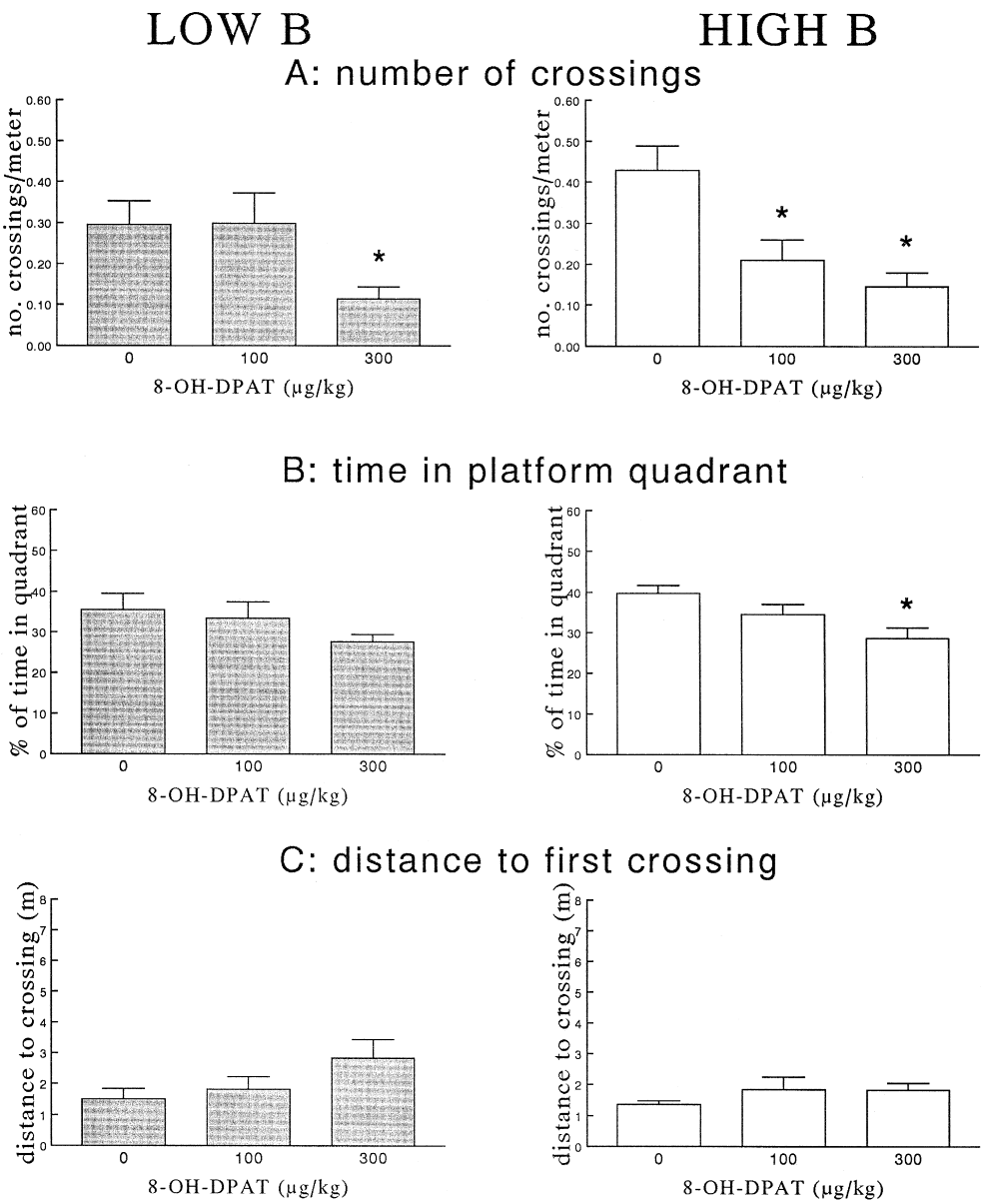

Fig. 3. Performance of Low B and High B rats in the free swim trial of the water maze, 30 min after injection of saline or 8-OH-DPAT. (A) Crossings of the former platform location. High B rats show higher sensitivity for 8-OH-DPAT. (B) Time spent in the former platform quadrant. 300 μg/kg 8-OH-DPAT leads to a significantly decreased persistence in High B animals, but not in Low B rats. (C) Distance swum up to first crossing of the former platform position. No statistically significant effect of 8-OH-DPAT. $* P < 0.05$.

were dissected from the cranium and frozen in isopentane on a mixture of ethanol and dry ice (-42°C), in order to measure 5-HT_{1A} receptor binding by in vitro autoradiography using [^{3}H]8-OH-DPAT. Both the radio-immunoassay for corticosterone determination and autoradiography procedures have been described previously (Veldhuis et al., 1982; Meijer et al., 1997).

2.6. Statistics

Data were analysed by one-way analysis of variance (ANOVA) followed by a post-hoc Tukey test. Significance was accepted at $p < 0.05$. Figs. 2 and 3 present means $\pm$ S.E.M.

3. Results

3.1. Intact rats

Fig. 2 shows that 8-OH-DPAT influences various parameters of the free swim trial. Significant main effects for intact rats were found for percentage of time spent in the former platform quadrant ($F(2,24) = 4.354$; $P = 0.024$) and total distance swum ($F(2,24) = 8.604$; $P = 0.02$).

Number of crossings of the former platform location per travelled metre ($F(2,24) = 2.754$; $P = 0.084$) and the distance swum until the first crossing ($F(2,24) = 1.848$; $P = 0.179$) just exceeded statistical significance.

Injection of 100 μg/kg and of 300 μg/kg 8-OH-DPAT led to a significantly increased total distance swum (Fig. 2D; $P < 0.05$). As shown in Fig. 2B, the dose of 100 μg/kg 8-OH-DPAT led to a significant decrease in the time spent in the former platform quadrant ($P < 0.05$). The number of crossings of the former platform position (Fig. 2A) was significantly lower in the 100 μg/kg ($P < 0.05$) but not the 300 μg/kg 8-OH-DPAT group ($P = 0.168$). Although the distance swum up to the first crossing of the platform position was somewhat longer in 8-OH-DPAT-treated animals (Fig. 2C), the difference was not statistically significant, indicating good retrieval of the acquired escape task.

The plasma corticosterone levels in saline-treated rats were slightly above basal levels (sham-saline: 4.9 ± 0.5 μg/dl). 8-OH-DPAT led to a clear and significant increase in plasma corticosterone levels (sham-100 μg/kg 8-OH-DPAT: 14.2 ± 0.5 μg/dl and sham-300 μg/kg 8-OH-DPAT 17.5 ± 1.7 μg/dl).

3.2. Adrenalectomized, corticosterone-substituted rats

3.2.1. Swimming patterns

Significant main effects in the free swim trial (Fig. 3) were found for percentage of time spent in the former platform quadrant ($F(5,59) = 2.825$; $P = 0.024$), the number of crossings of the former platform location per metre travelled ($F(5,59) = 6.66$; $P < 0.001$), and total distance swum ($F(5,59) = 10.77$; $P < 0.001$). No significant main effect was found for the distance swum up to the first crossing. The effect of 100 μg/kg 8-OH-DPAT on the swim patterns of rats of the High B group is illustrated in Fig. 4.

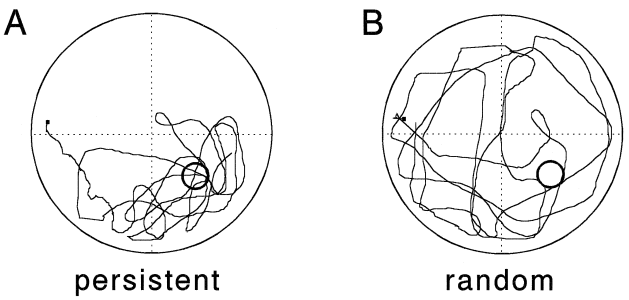

Fig. 4. Representative swimming patterns of rats in the free swim trial in the Morris water maze. The black square indicates the starting position of the rat, the circle in the lower right quadrant, the former position of the platform. Both rats are from the High B group, i.e., adrenalectomized, implanted with a corticosterone pellet and treated with a dose of 1 mg/kg corticosterone 90 min prior to the trial. (A) Saline-injected rat: the animal is persistent in its search behaviour and returns often to the former platform position. (B) Rat injected with 100 μg/kg 8-OH-DPAT 30 min prior to the trial: the animal displayed a random search pattern, although it swam directly to the former platform location at the start of the trial.

Table 1
Distance swum in metres (mean ± S.E.M.) after saline or 8-OH-DPAT injection during the 60 s free swim trial

	Low B	High B
Saline	10.9 ± 0.6	9.9 ± 0.6
100 μg/kg 8-OH-DPAT	13.7 ± 0.6[a]	13.2 ± 0.4[a]
300 μg/kg 8-OH-DPAT	14.0 ± 0.6[a]	14.2 ± 0.5[a]

[a] Significantly different from saline-treated animals $p < 0.01$.

8-OH-DPAT leads to increased locomotor activity regardless of corticosteroid receptor occupancy.

Low B animals were relatively insensitive to the search strategy-related effects of 8-OH-DPAT. Injection of 100 μg/kg 8-OH-DPAT had no effect on the search strategy of these animals when compared to the saline treatment (Fig. 3A,B). Injection of 300 μg/kg 8-OH-DPAT led to a significant decrease in the number of crossings (Fig. 3A), but not to a statistically significant decrease in time spent in the platform quadrant ($P = 0.201$; Fig. 3B).

In the High B group, saline-treated animals showed a trend to an increased number of crossings as compared to saline-treated Low B animals ($P = 0.071$; Fig. 3A).

High B animals showed a higher sensitivity to the search strategy-related effects of 8-OH-DPAT, than did the rats from the Low B group. Injection of 100 μg/kg and 300 μg/kg 8-OH-DPAT to High B animals led to a significant decrease in the number of crossings (Fig. 3A) and to a significantly lower percentage of time spent in the platform quadrant (Fig. 3B).

Irrespective of the corticosterone level, injection of 100 μg/kg and of 300 μg/kg led to a significantly increased total distance swum (Table 1). In none of the groups was there a statistically significant effect of 8-OH-DPAT on the distance swum up to the first crossing of the platform position, indicating good retrieval of the acquired escape task (Fig. 3C).

3.2.2. Corticosterone levels and 5-HT_{1A} receptor expression

The plasma corticosterone levels of the Low and High B groups were 2.1 ± 1.27 μg/dl and 27.8 ± 5.5 μg/dl, respectively, immediately after the free swim trial, i.e., 90 min after injection of vehicle or corticosterone. Analysis of autoradiograms of 20 μm sections of the dorsal hippocampus of saline-treated animals of the Low B and High B group after incubation with 0.5 nM [^{3}H]8-OH-DPAT showed no effect of B treatment on binding to hippocampal 5-HT_{1A} receptors (data not shown).

4. Discussion

The results of these experiments showed that the responsiveness of distinct 5-HT_{1A} receptor populations are under differential control by corticosterone in vivo. Ani-

mals with a predominant occupation of mineralocorticoid receptors by low, and constant, levels of corticosterone exhibited an attenuated 5-HT_{1A} receptor-mediated response related to the spatial search strategy in the water maze. An injection of corticosterone which causes activation of both corticosteroid receptor types enhanced the responsiveness of the rats to stimulation of the 5-HT_{1A} receptors involved in this behaviour. 8-OH-DPAT-induced locomotor activation was comparable under conditions of differential occupation of central corticosteroid receptors.

Administration of 8-OH-DPAT to intact animals interferes with acquisition of the Morris water maze task via postsynaptic hippocampal 5-HT_{1A} receptors (Carli and Samanin, 1992; Carli et al., 1992, 1995), presumably via hyperpolarizing effects (Beck and Goldfarb, 1985; Andrade and Nicoll, 1987; Baskys et al., 1987). We tested the effect of 8-OH-DPAT in the free swim trial, i.e., on animals that had acquired the learning task. Intact rats may show longer latencies before the platform position is first reached after 8-OH-DPAT administration (Carli and Samanin, 1992; Hunter and Roberts, 1988). In the present study, this effect was only seen as a trend in intact rats that received the high dose of 8-OH-DPAT, presumably due to large individual variations. No effect on this parameter was observed in adrenalectomized, corticosterone-replaced rats. This could have resulted from the training regimen or changes in performance that were associated with the artificial corticosterone rhythms.

The effect of 8-OH-DPAT on maze performance was restricted to a change in the strategy adopted after the first crossing of the platform position. Intact rats showed a mild reduction in persistent search behaviour under the present conditions. Animals that received a high dose of corticosterone 1 h before 8-OH-DPAT were more sensitive in this respect, than rats with constant low levels of corticosterone. There is no direct proof for the involvement of the hippocampus in the determination of the strategy adopted in the free swim trial. However, both acquisition and strategy choice in the absence of a platform reflect a reaction to a novel situation, in contrast to pure retrieval tasks. Moreover, specific mineralocorticoid receptor antagonists are able to influence the escape strategy of rats in the free swim trial (Oitzl and De Kloet, 1992). Mineralocorticoid receptors have a limited distribution in the brain and are mainly restricted to limbic regions like the septal–hippocampal area (Reul and De Kloet, 1985), a fact which further implies involvement of the hippocampus in search/escape strategies.

The approach used in this experiment was to mimic differential corticosteroid receptor occupancy, as was done in in vitro experiments using hippocampal slices, in which the responsiveness to 5-HT_{1A} receptor stimulation of CA1 pyramidal neurons was studied. From these in vitro studies, it has become clear that predominant mineralocorticoid receptor occupation (by low levels of corticosterone) leads to suppression of the 5-HT_{1A} receptor-mediated hyperpolarization (Joëls et al., 1991). Occupation of both mineralo- and glucocorticoid receptors by high levels of corticosterone leads to large 5-HT_{1A} receptor-mediated hyperpolarization (Joëls and De Kloet, 1992). Moreover, the response of the CA1 neurons in vitro is determined by the plasma corticosterone levels in vivo in the animal from which the hippocampal slice is obtained (Hesen and Joëls, 1996). The similar hormonal dependence of the 5-HT_{1A} receptor responses in this in vivo experiment is consistent with interference of 8-OH-DPAT with the search/escape strategy via postsynaptic hippocampal 5-HT_{1A} receptors. Future studies using specific ligands for mineralo- and glucocorticoid receptors will add further information about the involvement of the two corticosteroid receptors subtypes in this behavioural response.

Our results suggest that transient high concentrations of corticosterone can repair the deficient hippocampal responsiveness to 5-HT_{1A} receptor activation in animals that have predominant mineralocorticoid receptor occupation. The difference observed between rats from Low B and High B groups is due to effects of corticosterone that took place within 90 min, i.e., the time between administration of corticosterone and behavioural testing. Corticosterone can suppress levels of 5-HT_{1A} receptor mRNA within a few hours (Zhong and Ciaranello, 1995; Meijer and De Kloet, 1995). However, due to the long half-life of receptor protein (Pinto and Battaglia, 1994) it is not probable that a suppressive effect on mRNA levels is reflected within a few hours by a decreased amount of actual binding sites. Consistent with this assumption, we observed no differences in the binding of 0.5 nM [^{3}H]8-OH-DPAT between animals from Low B and High B groups.

Intact rats showed some effect of 8-OH-DPAT on performance in the free swim trial. Testing was performed in the morning, when corticosterone levels are low, and these were only mildly elevated immediately after the free swim trial. Thus, the intact animals appear to be more comparable in terms of corticosteroid receptor occupancy to the Low B group than to the High B group. In fact, both doses of 8-OH-DPAT increased the plasma level of corticosterone substantially, most probably occupying both corticosteroid receptors. Apparently, the intact animals represent an experimental condition between Low B and High B animals.

It is tempting to relate a possible function of the increased responsiveness to 5-HT_{1A} receptor activation to stress-induced rises in plasma corticosterone levels. Just as glucocorticoid receptor activation is a necessary condition for increased turnover of 5-HT in response to stress (Singh et al., 1992; Gemma et al., 1994), activation of glucocorticoid receptors could be needed to achieve postsynaptic responsiveness to the increased 5-HT release after stress. The magnitude of hippocampal 5-HT_{1A} receptor-mediated responses under resting conditions is suppressed via mineralocorticoid receptor-mediated processes: attenuation of the responsiveness to receptor activation and suppression

of the expression level of the 5-HT_{1A} receptor themselves (Biegon et al., 1985; Chalmers et al., 1993; Kuroda et al., 1994; Meijer and De Kloet, 1995). Such a scenario would indicate that suppression of hippocampal 5-HT_{1A} receptor activation is involved in the initial response of the animals to a stressor, while activation of the raphe–hippocampal pathway forms part of the (behavioural) adaptation after a stressful stimuli (De Kloet, 1995).

In conclusion, our present data show that 5-HT_{1A} receptors related to spatial search strategy are under differential control of low and high levels of corticosterone. In adrenalectomized rats chronically supplemented with low levels of corticosterone, the sensitivity of these 5-HT_{1A} receptor-mediated responses is lower than in animals that were treated with a high dose of corticosterone 60 min before 8-OH-DPAT injection. There is a striking parallel between the hormonal dependence of the 5-HT_{1A} receptor-mediated effects on spatial search strategy on the one hand, and the magnitude of 5-HT_{1A} receptor-mediated hyperpolarization of CA1 pyramidal cells in vitro on the other hand. The results suggest that hippocampal 5-HT_{1A} receptor-mediated responses are attenuated by mineralocorticoid receptor-mediated effects of corticosterone in vivo, and that this effect can be over-ruled by action of high corticosterone that involves additional activation of glucocorticoid receptors.

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References

Andrade, R., Nicoll, R.A., 1987. Pharmacologically distinct actions of serotonin on single pyramidal neurones of the rat hippocampus recorded in vitro. J. Physiol. 394, 99–124.

Arvidsson, L.E., Hacksell, U., Nilsson, J.L.G., Hjorth, S., Carlsson, A., Lindberg, P., Sanchez, D., Wikstrom, H., 1981. 8-Hydroxy-2-(di-*n*-propylamino)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. J. Med. Chem. 24, 921–923.

Baskys, A., Niesen, C.E., Carlen, P.L., 1987. Altered modulatory actions of serotonin on dentate granule cells of aged rats. Brain Res. 419, 112–118.

Beck, S.G., Goldfarb, J., 1985. Serotonin produces a reversible concentration dependent decrease of population spikes in rat hippocampal slices. Life Sci. 36, 557–563.

Biegon, A., Rainbow, T.C., McEwen, B.S., 1985. Corticosterone modulation of neurotransmitter receptors in rat hippocampus: a quantitative autoradiographic study. Brain Res. 332, 309–314.

Carli, M., Samanin, R., 1992. 8-Hydroxy-2-(di-*n*-propylamino)tetralin impairs spatial learning in a water maze: role of postsynaptic 5-HT_{1a} receptors. Br. J. Pharmacol. 105, 720–726.

Carli, M., Lazarova, M., Tatarczynska, E., Samanin, R., 1992. Stimulation of 5-HT_{1a} receptors in the dorsal hippocampus impairs acquisition and performance of a spatial task in a water maze. Brain Res. 595, 50–56.

Carli, M., Luschi, R., Garofalo, P., Samanin, R., 1995. 8-OH-DPAT impairs spatial but not visual learning in a water maze by stimulating 5-HT_{1A} receptors in the hippocampus. Behav. Brain Res. 67, 67.

Chalmers, D.T., Watson, S.J., 1991. Comparative anatomical distribution of 5-HT_{1A} receptor mRNA and 5-HT_{1A} binding in the rat brain—a combined in situ hybridisation/in vitro receptor autoradiographic study. Brain Res. 561, 51–60.

Chalmers, D.T., Kwak, S.P., Mansour, A., Akil, H., Watson, S.J., 1993. Corticosteroids regulate brain hippocampal 5-HT_{1A} receptor mRNA expression. J. Neurosci. 13, 914–923.

De Kloet, E.R., 1995. Steroids, stability and stress. Front. Neuroendocrinol. 16, 416–425.

Fuller, R.W., 1992. The involvement of serotonin in regulation of pituitary–adrenocortical function. Front. Neuroendocrinol. 13 (3), 250–270.

Gemma, C., De Luigi, A., De Simoni, M.G., 1994. Permissive role of glucocorticoids on interleukin-1 activation of the hypothalamic serotonergic system. Brain Res. 651, 169–173.

Hesen, W., Joëls, M., 1996. Modulation of 5-HT_{1A} responsiveness in CA1 pyramidal neurons by in vivo activation of corticosteroid receptors. J. Neuroendocrinol. 8, 433–438.

Hunter, A.J., Roberts, F.F., 1988. The effects of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) on spatial learning in the Morris water maze task. In: Dourish, C.T., Ahlenius, S., Hutson, P.H. (Eds.), Brain 5-HT_{1A} Receptors: Behavioural and Neurochemical Pharmacology. Horwood, Chichester, p. 278.

Joëls, M., De Kloet, E.R., 1992. Coordinative mineralocorticoid and glucocorticoid receptor-mediated control of responses to serotonin in rat hippocampus. Neuroendocrinology 55, 344–350.

Joëls, M., Hesen, W., De Kloet, E.R., 1991. Mineralocorticoid hormones suppress serotonin responses in rat hippocampus. J. Neurosci. 11, 2288–2294.

Kuroda, Y., Watanabe, Y., Albeck, D.S., Hastings, N.B., McEwen, B.S., 1994. Effects of adrenalectomy and type I or type II glucocorticoid receptor activation on 5-HT_{1A} and 5-HT_2 receptor binding and 5-HT transporter mRNA expression in rat brain. Brain Res. 648, 157–161.

Meijer, O.C., De Kloet, E.R., 1995. A role for the mineralocorticoid receptor in a rapid and transient suppression of 5-HT_{1A} receptor mRNA by corticosterone. J. Neuroendocrinol. 7, 653–657.

Meijer, O.C., Oitzl, M.S., De Kloet, E.R., 1994. Adrenalectomy leads to a different responsiveness to 8-OH-DPAT in a water-maze learning task. In: de Kloet, E.R., Azmitia E.C., Landfield, P.W. (Eds.), Ann. NY Acad. Sci., 746, pp. 408–410.

Meijer, O.C., Van Oosten, R.V., De Kloet, E.R., 1997. Elevated diurnal trough concentrations of corticosterone suppress hippocampal 5-HT_{1A} receptor expression in adrenally intact rats: implication for the pathogenesis of depression. Neuroscience 80, 419–426.

Morris, R.G.M., Garrud, P., Rawlins, J.N.P., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297, 681–683.

Oitzl, M.S., De Kloet, E.R., 1992. Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. Behav. Neurosci. 106, 62–71.

Pinto, W., Battaglia, G., 1994. Comparative recovery kinetics of 5-hydroxytryptamine 1A, 1B and 2A receptor subtypes in rat cortex after receptor inactivation: evidence for differences in receptor production and degradation. Mol. Pharmacol. 48, 1111–1119.

Pompeiano, M., Palacios, J.M., Mengod, G., 1992. Distribution and cellular localization of mRNA coding for the 5-HT_{1A} receptor in the rat brain: correlation with receptor binding. J. Neurosci. 12, 440–453.

Reul, J.M.H.M., De Kloet, E.R., 1985. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology 117, 2505–2511.

Reul, J.M.H.M., Van den Bosch, J.R., De Kloet, E.R., 1987. Relative occupation of type-I and type-II corticosteroid receptors in the rat brain following stress and dexamethasone treatment: functional implications. J. Endocrinol. 115, 459–467.

Singh, V.B., Phan, T.-H., Corley, K.C., Boadle-Biber, M.C., 1992.

Increase in cortical and midbrain tryptophan hydroxylase activity by intracerebroventricular administration of corticotropin releasing factor: block by adrenalectomy, by RU 38486 and by bilateral lesions to the central nucleus of the amygdala. Neurochem. Int. 20, 81–92.

Spencer, R.L., Miller, A.H., Moday, H., Stein, M., McEwen, B.S., 1993. Diurnal differences in basal and acute stress levels of type I and type II adrenal steroid receptor activation in neural and immune tissues. Endocrinology 133, 1941–1950.

Van Eekelen, J.A.M., Jiang, W., De Kloet, E.R., Bohn, M.C., 1988. Distribution of the mineralocorticoid and the glucocorticoid receptor mRNAs in the rat hippocampus. J. Neurosci. Res. 21, 88–94.

Van Steensel, B., Van Binnendijk, E.P., Hornsby, C.D., Van der Voort, H.T.M., Krozowski, Z.S., De Kloet, E.R., Van Driel, R., 1996. Partial colocalization of glucocorticoid and mineralocorticoid receptors in compartments in nuclei of rat hippocampal neurons. J. Cell Sci. 109, 787–792.

Veldhuis, H.D., Van Koppen, C., Van Ittersum, M., De Kloet, E.R., 1982. Specificity of adrenal steroid receptor system in the rat hippocampus. Endocrinology 110, 2044–2051.

Zhong, P., Ciaranello, R.D., 1995. Transcriptional regulation of hippocampal 5-HT_{1A} receptors by corticosteroid hormones. Mol. Brain Res. 29, 23–34.