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11β-Hydroxysteroid dehydrogenase functions reversibly as an oxidoreductase in the rat hippocampus in vivo

Peter H. Jellinck[a,1], Constantine Pavlides[a], Randall R. Sakai[b], Bruce S. McEwen[a,*]

[a]*Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10021, USA*
[b]*Department of Animal Biology, University of Pennsylvania, Philadelphia, PA 19104, USA*

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Abstract

The localization in the brain and metabolism of ^{3}H-labeled corticosterone (B) and 11-dehydrocorticosterone (A) of high specific radioactivity was determined after stereotaxic injection into the hippocampus of anesthetized rats. [^{3}H]B was cleared very rapidly with, on average, only about 7% being recovered after 5 min and 0.5% after 30 min. Most of this ^{3}H-radioactivity was localized in the area surrounding the site of injection with little diffusion to adjacent areas. These findings make it possible to compare the short term metabolism of [^{3}H]A and [^{3}H]B in different lobes of the hippocampus in the same animal and establish their local equilibrium point in vivo. Under these conditions, about 5% conversion of each steroid to the other was observed in contrast to the situation in cultured hippocampal cells where 11β-hydroxysteroid dehydrogenase (11-HSD) has been shown by others to act primarily as a reductase catalyzing the conversion of A to B. This method can also be used to study the effect of inhibitors such as 11α-hydroxyprogesterone, applied locally in the brain, on the metabolism of corticosteroids. The rate of conversion [^{3}H]B or [^{3}H]A to their dihydro- and tetrahydro-derivatives capable of modulating the $GABA_a$ receptor in the hippocampus was much lower than their interconversion. Thus, factors which influence the direction of the 11-HSD catalyzed reaction are important in regulating not only salt appetite and blood pressure but also the levels of neuroactive metabolites of corticosterone.

1. Introduction

Corticosteroids play an important role in coordinating many physiological functions both in peripheral tissues and in the central nervous system [1,2]. In the brain, they are involved in neuronal and glial development and survival [3] as well as in the regulation of blood pressure [4]. Corticosterone (B) can be converted to its inert 11-keto derivative, 11-dehydrocorticosterone (A), by the enzyme 11β-hydroxysteroid dehydrogenase (11-HSD) which exists in 2 main isoforms. 11-HSD1 is an NADP(H)-dependent oxidoreductase with relatively low affinity for B ($K_m \backsim 10$ μM) expressed principally in glucocorticoid target tissues such as the liver, lung, testis, pituitary and brain while 11-HSD2 is an NAD-dependent dehydrogenase with a higher affinity for B ($K_m = 10$–25 nM) found mainly in aldosterone target tissues (kidney, salivary glands and colon), the female reproductive system (ovary, uterus and placenta) and the adrenals [5–9]. This tissue-specific pattern of distribution can be correlated with their physiological roles. Thus, 11-HSD1 acts reversibly either by inactivating B by conversion to A or generating B from A thereby modulating corticosteroid action [10–12]. On the other hand, 11-HSD2 allows aldosterone to exert its specific function in mineralocorticoid target tissues in the presence of a large excess of B which it converts to A [13–15].

In the central nervous system which contains very little of the type 2 isoform [16], HSD-1 has to carry out both the protective and regulatory roles of this enzyme. Chronic excess of corticosteroids, as well as repeated stress, leads to atrophy of dendrites and loss

* Corresponding author. Fax: +1-212-327-8634.
[1] Present address: Department of Biochemistry, Queen's University, Kingston, Ont., Canada K7L 3N6

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of pyramidal neurons, while lack of corticosteroids causes dentate gyrus neurons to undergo programmed cell death as well as stimulating the replacement of neurons via localized neurogenesis [1,17–20]. This raises the question of whether 11-HSD1 is acting oxidatively as a dehydrogenase or as a reductase in this brain region under normal physiological conditions. In this paper we have demonstrated that 11-HSD functions reversibly as an oxidoreductase when very low levels (0.4–15 ng) of ^{3}H-labeled corticosterone or 11-dehydrocorticosterone are infused into the hippocampus or amygdala of anesthetized rats. We have also studied the rate of metabolism of A and B in these brain regions and shown that, although these steroids are cleared rapidly, they do not diffuse significantly into adjacent areas. This provides a useful technique for studying the oxidation of B on one side and the reduction of A on the other side of the hippocampus within the same animal. It can also be used to evaluate the effect of inhibitors using the contralateral lobe as control. In addition, we have applied this method to determine the rate of formation of the ring A and B reduced steroids known to have neuroactive effects by modulating the $GABA_a$ receptor [21,22].

2. Materials and methods

2.1. Materials

[1,2,6,7-^{3}H]B (88 Ci/mmol) was purchased from New England Nuclear (Boston, MA) while [1,2,6,7-^{3}H]A with the same specific radioactivity, was a generous gift from M. Hardy (Population Council, The Rockefeller University, New York). The unlabeled corticosteroids were from Steraloids (Wilton, NH) or from Sigma Chemical Co. (St Louis, MO) which also provided the coenzymes and inhibitors. All other chemicals were the purest available. The silica gel containing fluorescent indicator on aluminum sheets was supplied by Fisher Scientific Co. (Pittsburg, PA).

2.2. Animals

Adult male Sprague Dawley rats (250–350 g) from Charles River Laboratories were acclimatized for 5–7 days and housed in plastic cages (groups of 2 or 3 per cage) in the accredited animal facilities of Rockefeller University. The room was maintained at 25°C on a 12:12 h light/dark cycle (lights on at 7 a.m.) and the rats were provided with Purina rat chow and water ad libitum.

2.3. Intracerebral microinjection

The rats were deeply anesthetized with Nembutal (40 mg/kg) and bilateral burr holes drilled in the exposed skull for insertion of the injection needles (225 gauge) attached to 10 μl Hamilton syringes. They were directed to either the hippocampus (coordinates: A–P, $\beta = 4.0$ mm; M–L = ± 2.2 mm; D–V = -3.1 mm from the skull surface) or the amygdala (coordinates: A–P, $\beta = 2.8$ mm; M–L = ± 4.0 mm; D–V = -8.0 mm from the skull surface) with the coordinates according to Paxinos and Watson [23]. The ^{3}H-labeled steroids in 3–5 μl of ethanol were injected slowly over a period of 1 min to prevent any concentration build-up able to cause local tissue damage. The needle was left on location for another 30 s to minimize infusion of the administered compounds into the needle tract. In some experiments, the steroids were administered in saline, but ethanol was needed to investigate the effects of water-insoluble inhibitors at higher concentrations than [^{3}H]A and [^{3}H]B.

2.4. Brain dissection

The rats were decapitated at various time periods (5–30 min) after stereotaxic injection, the brains removed rapidly and dissected on a frosted glass plate on ice to obtain the hippocampus and amygdala. They were frozen immediately on dry ice and kept at −70°C until assayed for distribution and metabolism of the injected radioactive corticosteroids. Trunk blood was collected in heparinized tubes after decapitation and plasma obtained by centrifugation at $1000 \times g$ for 5 min.

2.5. Tissue preparation and extraction

The frozen brain areas were homogenized in ice-cold 0.1 M sodium phosphate (2 ml) pH 7.4 using a Potter–Elvehjem homogenizer with a Teflon pestle in the presence or absence of the potent 11β-hydroxysteroid dehydrogenase inhibitor — 11α-hydroxyprogesterone (11α-HP, 12.5 μg/ml) [24]. The homogenates were then extracted twice with equal volumes of diethyl ether for determination of ^{3}H-radioactivity and identification of corticosteroid metabolites as described below. In some experiments, the homogenate was also further extracted with ethyl acetate.

2.6. Identification of metabolites

A, B and the putative corticosteroid metabolites AH_2, AH_4, BH_2 and BH_4 (10 μg of each) were added to the ether extract to act as carrier and, after drying over anhydrous Na_2SO_4, the solvent was allowed to evaporate at room temperature in a fume hood. The steroids were then separated by TLC on silica gel containing fluorescent indicator using chloroform-acetone (4:1, by vol.). A and B were visualized at 312 nm and

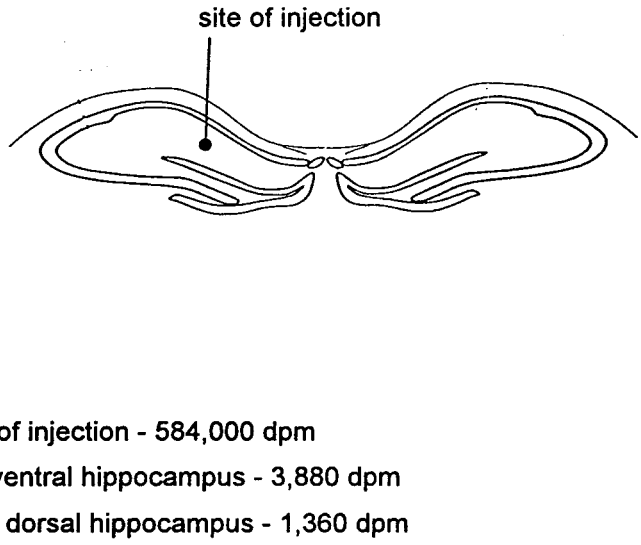

Fig. 1. Localization of ^{3}H-radioactivity in the hippocampus 30 min after injection of [^{3}H]B. The steroid (5.56×10^6 dpm in 9.8 ng) was injected into the left dorsal lobe of the hippocampus (expt. 1) and the areas indicated assayed for ^{3}H-radioactivity. Other conditions as described in the text.

the other metabolites, by spraying with nitro blue tetrazolium (0.5% w/v in ethanol) followed by methanolic NaOH (4% w/v) and heating on a hot plate. The appropriate areas were cut out, added to counting vials containing scintillation fluid (5 ml) and ^{3}H-radioactivity determined. No significant loss of ^{3}H (< 10%)occurred during these procedures.

3. Results

The localization of ^{3}H-radioactivity 30 min after the stereotaxically-guided injection of [^{3}H]B into the left lobe of the hippocampus is shown in Fig. 1. Most of this radioactivity was found in the area surrounding the site of injection with very little diffusion to the adjacent ventral hippocampus or the contralateral dorsal lobe.

Fig. 2 shows the distribution of ^{3}H-radioactivity recovered from the area of injection after homogenization in phosphate buffer (pH 7.4) followed by extraction with ether followed by ethyl acetate 5 and 30 min after administration of [^{3}H]B (ca. 6×10^6 dpm in 10 ng). After both time periods, ethyl acetate removed a further 50% (approx.) of the ^{3}H-radioactivity remaining in the ether-extracted aqueous medium while the aqueous residue would consist presumably of highly polar, possibly conjugated and protein-bound pro-

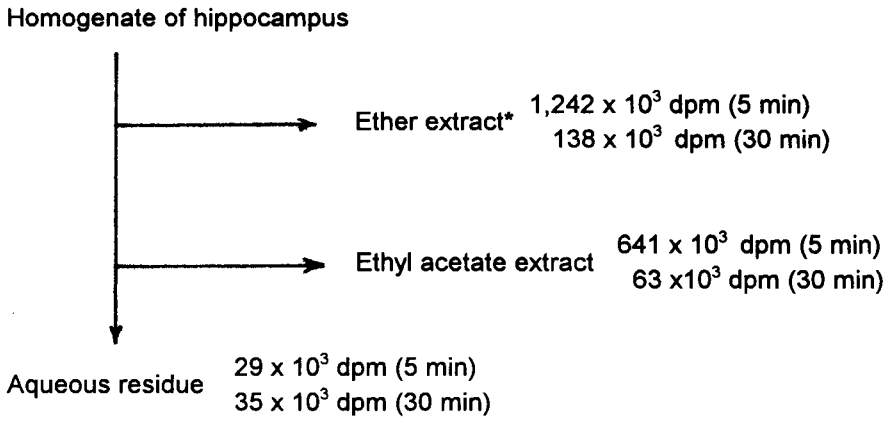

Fig. 2. Distribution of ^{3}H-radioactivity after extraction of hippocampal homogenates with organic solvents. Rats were exposed to [^{3}H]B (6.60×10^6 dpm in 11.7 ng) for 5 min or [^{3}H]B (5.56×10^6 dpm in 9.8 ng) for 30 min and homogenates of the area around the site of injection extracted with ether followed by ethyl acetate for determination of ^{3}H-radioactivity. *components were separated by TLC and assayed for ^{3}H-radioactivity (Table 1).

Table 1
Metabolism of ^{3}H-labeled corticosterone (B) and 11-dehydrocorticosterone (A) injected stereotaxically into rat brain regions[a]

Expt. no.	Brain area	^{3}H-steroid administered (dpm × 10^{-3})	Period of exposure (min)	^{3}H-radioactivity recovered (dpm × 10^{-3})						A ⇄ B (%)
				B	A	BH_2	BH_4	AH_2	AH_4	
1	l. Hippo	[^{3}H]B (5560)	30	36.4	1.03	0.46	0.19	0.30	0.16	B → A 2.8
2	l. Hippo	[^{3}H]B (6600)	5	789	14.6	1.9	2.00	2.07	3.04	B→ A 1.9
	Plasma	[^{3}H]B	5	26.5	1.40	0.27	0.27	0.02	0.02	B→ A 5.3
3	l. Hippo	[^{3}H]B (8400)	5	484	9.53	10.2	3.25	5.90	1.55	B→ A 2.0
	r. Hippo	[^{3}H]B	30	33.9	0.55	0.53	0.22	0.36	0.20	B→ A 1.6
	Plasma	[^{3}H]B	30	9.8	1.19	0.41	0.29	0.19	0.31	B→ A 12.1
4	l. Hippo	[^{3}H]B (655)	5	6.8	0.32	0.14	0.11	0.05	0.08	B→ A 4.7
	r. Hippo	[^{3}H]A (627)		0.83	16.9	0.12	0.14	0.56	0.22	A→ B 4.9
5	l. Hippo	[^{3}H]B (251)	5	13.6	0.64	0.22	0.33	0.11	0.18	B→ A 4.7
	r. Hippo	[^{3}H]A (245)		0.26	8.3	0.23	0.08	0.88	0.10	A→ B 3.1
6	l. Hippo	[^{3}H]B (523)	5	75.9	2.03	1.36	1.01	0.29	0.49	B→ A 2.7
	r. Hippo	[^{3}H]B + (523) + 11αHP (100 μg)		53.9	0.32	0.91	0.72	0.21	0.31	B→ A 0.6
7	l. Hippo	[^{3}H]A (272)	5	0.30	7.3	0.37	0.06	0.24	0.07	A→ B 4.1
	r. Hippo	[^{3}H]A (272) + 11α-HP (100 μg)		0.29	20.2	1.01	0.11	0.70	0.11	A→ B 1.4
8	l. Hippo	[^{3}H]B (261) saline	10	11.9	0.84	0.17	0.16	0.08	0.10	B→ A 7.0
	r. Hippo	[^{3}H]A (246) saline		0.48	6.94	0.25	0.10	0.21	0.07	A→ B 6.9
9	l. Hippo	[^{3}H]B (413)	5	25.0	1.13	0.35	0.45	0.12	0.21	B→ A 4.5
	r. Amyg	[^{3}H]B (413)		19.4	0.96	0.29	0.22	0.08	0.15	B→ A 4.9

[a] The ^{3}H-steroids (0.43–14.8 ng) were injected into the hippocampus (Hippo) or amygdala (Amyg) of anesthetized adult male rats and the animals killed after various time periods. The appropriate brain regions were removed, homogenized in phosphate buffer (0.1 M) pH 7.4 and extracted with ether for separation of metabolites by TLC and radioassay. Other conditions are described in the text. AH_2, BH_2, AH_4 and BH_4 are the 5α-dihydro- or the 3α,5α-tetrahydro-derivatives of A or B.

ducts. Homogenization of the tissue in buffer containing 11α-HP (25 μg/ml) to prevent any possible interconversion of [^{3}H]A and [^{3}H]B in the homogenate during this short period (< 1 min) before extraction with ether did not alter the in vivo results obtained in the absence of this 11-HSD inhibitor.

[^{3}H]B was cleared very rapidly with only about 7% being recovered unchanged after 5 min and about 0.5% after 30 min (Table 1). A, the C11-oxidized derivative of B, accounted for only 3–5% of the injected steroid while the C3 and C5 reduced products of A and B were present in even lower amounts. The TLC system used (chloroform–acetone 4:1) was able to separate all the reduced metabolites from A and B without overlap. The ratio of ^{3}H-radioactivity in A relative to B after both 5 and 30 min was higher in the plasma than in the hippocampus (Table 1, expt. 2 and 3) but would include peripheral interconversion. Examining the plasma for metabolites when [^{3}H]A or [^{3}H]B had its counterpart or an inhibitor injected into the contralateral lobe of the same animal would provide no meaningful information.

With [^{3}H]A, available only in small amounts but with the same specific radioactivity as [^{3}H]B, smaller but equivalent quantities of each were injected into the hippocampus (or amygdala) to obtain comparable results (Table 1, expts. 4–8). In all 5 cases, the conversion of A → B and B → A were similar and averaged around 5% (4.75 ± 0.80 and 4.72 ± 0.68 SEM). No substantial difference in the metabolism of [^{3}H]B by the hippocampus and amygdala was observed (Table 1, expt. 9) and the 11β-hydroxysteroid dehydrogenase inhibitor, 11α-hydroxyprogesterone (11α-HP), was effective with both substrates reducing the conversion of [^{3}H]B to [^{3}H]A from 4.0% to 0.6% and that of [^{3}H]A to [^{3}H]B from 4.1% to 1.4%. Using saline in place of ethanol as vehicle for administering the ^{3}H-labeled steroid did not alter the metabolic interconversion of [^{3}H]A and [^{3}H]B (Table 1, expt. 8).

4. Discussion

Recently, Seckl and coworker [11,12] have shown that the bidirectional enzyme 11β-hydroxysteroid dehydrogenase (11-HSD1) acts primarily as a reductase in both rat hepatocytes and cultured hippocampal cells by catalyzing the conversion of A to B. This was in contrast to the situation in homogenates which showed plentiful dehydrogenase (oxidative) activity. Originally, it had been proposed that the induction of 11-HSD observed in the hippocampus after stress or the chronic administration of dexamethasone may protect neurons from the deleterious effects of glucocorticoid excess by oxidizing B to A [25,26]. However, it now appears that 11-HSD can have a reductive role, increasing rather than attenuating the effects of chronic corticosteroid overexposure. This is supported

by experiments showing that the potentiating effect of A on kainate neurotoxicity in hippocampal cell cultures could be prevented by inhibiting 11-HSD with carbenoxolone [12].

Our current experiments were designed to confirm and extend these observations on corticosteroid metabolism in the hippocampus (and other brain areas) in vivo. The approach was to measure the actual interconversion of A and B and the formation of their ring A and B reduced metabolites in intact rats when very small amounts (0.4–15 ng) of ^{3}H-labeled A or B of high specific radioactivity were infused directly into the hippocampus. However, our results with intact animals differ from those obtained by Seckl and coworkers [12] with hippocampal cells in which reductase activity, namely conversion of A to B, predominated. We found that an equilibrium point (about 5% conversion) was reached when the lower levels (0.4–1.0 ng) of either [^{3}H]A or [^{3}H]B were infused in vivo. The rapid extraction of the homogenized tissue in ice-cold buffer with ether is unlikely to produce artifactual results in the short time period (<1 min) needed for these procedures as demonstrated by previous in vitro incubations (not shown) or by homogenizing in the presence of the 11-HSD inhibitor, 11α-hydroxyprogesterone.

The findings imply that corticosteroid metabolism in the hippocampus is in balance between the oxidized and reduced forms of the steroid although this equilibrium might be shifted by the redox state of the tissue or other factors which influence the direction of the 11-HSD-catalyzed reaction. It is known that both a lack and an excess of corticosteroids can influence the survival of hippocampal neurons [19,20]. It also means that 11-HSD provides a major control point in the hippocampus for the subsequent formation of the dihydro and tetrahydro derivatives. These neuroactive steroids, capable of modulating the $GABA_a$ receptor [21,22], are formed in much lower amounts from either A or B. However, 11-HSD cannot play a role in regulating the formation of the active reduced metabolites of progesterone or deoxycorticosterone (DOC) lacking an 11-hydroxy group or of aldosterone in its hemiacetal form.

The steroids were given by stereotaxically-guided injection and their distribution, localization and metabolism determined after various time intervals. The clearance rates were high with considerable ^{3}H-radioactivity appearing in the plasma within 5 min even though that which remained in the brain was localized near the site of injection with little diffusion to nearby areas. Thus, when [^{3}H]B was injected into the dorsal region of the left lobe of the hippocampus very little radioactivity was found in the adjacent ventral hippocampus or in the contralateral right lobe. This lack of diffusion over a short time period was taken advantage of to study the metabolism of [^{3}H]A and [^{3}H]B injected into different hippocampal lobes of the same rat and to establish that an equilibrium position of about 5% interconversion is attained. The effect of 11α-HP injected locally into the same animal with the contralateral side of the hippocampus acting as control, was shown to inhibit 11-HSD in that lobe only and this technique might also be applied to studying the action of inhibitors of 5α-reductase or 3α-hydroxysteroid dehydrogenase. It should also make it possible to correlate in situ changes in the metabolism of [^{3}H]A and [^{3}H]B under various physiological conditions including those which increase salt appetite or blood pressure [27].

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