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Short communication

The polyamine stress response: tissue-, endocrine-, and developmental-dependent regulation

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Abstract

Transient alterations in polyamine (PA) metabolism, termed the polyamine stress response (PSR), constitute a common cellular response to stressful stimuli. In contrast to the adult brain and liver, the PSR in the adrenal gland and thymus is characterized by a reduction in PA metabolism. The brain PSR undergoes an early postnatal period of non-responsiveness. The aim of the present study was twofold: i) to determine whether the PSR in the liver, thymus, and adrenal gland is developmentally regulated as that in the brain and ii) to establish whether neuronal and hormonal signals can activate the PSR independently. Ornithine decarboxylase (ODC) activity and tissue PA concentrations served as markers of the PSR. Changes were measured in male Wistar rats during postnatal development and at 2 weeks after adrenalectomy in adults. Unlike the brain, the direction of the PSR in peripheral organs did not undergo developmental changes. After adrenalectomy, the PSR was not activated in the thymus and liver by acute (2-hr) restraint stress, but a characteristic PSR was induced in the hippocampus. However, dexamethasone injection (3 mg/kg) did induce a characteristic PSR in all organs of adrenalectomized rats. The results justify the following conclusions: i) Unlike peripheral organs, the PSR in the brain is developmentally regulated; ii) The developmental switch to a mature PSR in the brain corresponds in time to the cessation of the "stress hypo-responsive period" in the hypothalamic–pituitary–adrenocortical (HPA) axis; iii) In the periphery, the PSR appears to be dependent principally on stress-induced activation of the HPA axis and on increased circulating glucocorticoid concentrations rather than on neuronal activation; iv) In the brain, however, the PSR can be induced independently by glucocorticoids or by direct activation of the neuronal circuitry; and v) up-regulation of the PSR, as in the brain and liver, is constructive and may be implicated in cell survival, while its down-regulation, as in the adrenal and thymus, may be implicated in cell death.

Keywords: Adrenalectomy; Brain; Developmental regulation; Dexamethasone treatment; Liver; Ornithine decarboxylase activity; Putrescine; Restraint stress; Spermidine; Spermine; Thymus

1. Introduction

It has long been known that persistent exposure to stressors predisposes vulnerable individuals to affective disorders and exacerbates the symptoms in those who are already affected [1–4]. As with the general adaptation (stress) syndrome that elicits characteristic behavioral, physiological, and neuroendocrine changes in the affected organism [5], so do individual cells respond to life-threatening stressful stimuli by activating, via second messenger systems, a general intracellular "stress program." The inductive expression of a universal set of stress proteins [6,7] and a transient increase in PA metabolism, termed the PSR [8], are considered to be integral components of this cellular stress program. In the adult brain, the PSR is a common response to stressful stimuli, and its magnitude appears to be related to the intensity of the stressor [8]. In the extreme, traumatic stress can result in an incomplete brain PSR, with persistent accumulation of putrescine, the diamine precursor of PAs, and eventual reduction in the concentrations of the PAs, spermidine, and spermine [8,9]. These cellular changes are probably aimed at enhancing nerve cell survival [8,10] rather than contributory to cell death [9]. This anomaly in brain PA metabolism may occur during maturation as a result of specific developmental changes in regulation of gene expression [8].

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Abbreviations: PA, polyamine; PSR, polyamine stress response; HPA, hypothalamic–pituitary–adrenocortical; ODC, ornithine decarboxylase.

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Our previous studies have implicated the PSR as a molecular mechanism involved in the adaptive and/or maladaptive brain response to stressful events. We found that the repetitive application of stressors results in a recurrence of the PSR in the brain (but to habituation of the response in the periphery) and, interestingly, that the brain PSR, in contrast to the periphery, can be blocked by a long-term, but not short-term, treatment with lithium [11,12], the most efficacious treatment for manic-depressive illness. Proper regulation of brain PA metabolism, therefore, may be critical for an appropriate response to stressors.

The regulation of the PSR was found to be tissue-specific. Thus, in contrast to the adult brain and liver where PA metabolism is up-regulated by stressors, in the adrenal gland and thymus the PSR is down-regulated [13,14]. Down-regulation of the PSR is correlated with stress-induced degeneration in the thymus and, therefore, may be implicated in the process of cell death [15]. We have recently obtained evidence that in the rat brain, the PSR is developmentally regulated, switching from down-regulation or non-responsive mode to up-regulation at around 15 days of age depending on the brain region [16]. Interestingly, the switch to a mature brain PSR pattern coincides with the cessation of the stress hypo-responsive period in the HPA neuroendocrine system [17–19]. Therefore, the possibility that the brain PSR may be involved in the developmental switch of the HPA system to a stress-responsive mode is intriguing.

The aim of the present work was twofold. First, we sought to determine whether or not the PSR in the peripheral tissues under study (i.e. liver, thymus, and adrenal gland) is regulated similarly to that of the brain during development. Second, we wished to establish whether the PSR can be activated independently by neuronal or hormonal signals in the various tissues.

2. Materials and Methods

2.1. Principle of the study

Animals of different ages were treated with a single dexamethasone injection as a stress signal and measurements were done in tissues obtained 6 hr after the injection. Dexamethasone is a synthetic analog of the stress hormones, glucocorticoids, and is commonly used to study the stress-induced effects of glucocorticoids. Untreated and vehicle-injected animals served as controls. The adrenal glands of adult rats were extirpated in order to verify whether glucocorticoids are essential for the PSR. Adrenalectomized and sham-operated control animals were injected with dexamethasone or subjected to a single restraint stress session, and measurements were performed on tissues obtained 6 hr after the injection [20] or after the beginning of the application of the stressor. Animals left undisturbed in their home cages (unhandled) served as controls. Changes in ODC, the enzyme catalyzing the formation of putrescine in the first and rate-limiting step of PA biosynthesis [21], and in tissue PA concentrations served as markers of the PSR. The effects of stressors were measured in the hippocampus, a brain region known for its response to stressful stimuli [22], and in the liver, thymus, and adrenal gland.

2.2. Animals

The experiments were carried out with male Wistar rats. The animals were bred and grown according to NIH guidelines in the Institute's vivarium under temperature (21 ± 2°)-, humidity (55–75%)-, and light (12-hr light–dark cycle)-controlled conditions, with a free supply of food and water. A dam with a litter of 10 pups were housed in individual cages. Pups were chosen randomly and after treatments returned to their original home cages for the remainder period. Weaning was at 21 days of age and from then on animals were kept 4 to a cage.

2.3. Treatments

Dexamethasone 21-phosphate (3 mg/kg) from Sigma Israel was dissolved in saline (0.9% w/v NaCl) and injected intraperitoneally. For adrenalectomy, rats were anesthetized with halothane (2% in 100% O_2) and the two adrenal glands were removed through small incisions made on both sides of the back. Operated animals were maintained on saline as their drinking solution. For restraint stress, rats were placed for 2 hr, between 08:30 and 10:30 a.m., in cylindrical Plexiglas restrainers adapted for the animal size that prevent animals from turning around or reversing themselves.

2.4. Tissue dissections

Six hours after stressor application, the animals were decapitated and tissues were rapidly excised. The brain was dissected on a metal block over ice as reported previously [22]. The tissues were stored at −70° until assay, usually within 2 weeks.

2.5. ODC assay

The dissected tissues were homogenized in 5 volumes of ice-cold 50 mM Tris–HCl buffer, pH 7.5, containing 5 mM dithiothreitol and 40 μM pyridoxal-5′-phosphate. The activity of ODC was assayed in the tissue homogenates according to the $^{14}CO_2$ evolving method, as previously reported [23].

2.6. PA concentration measurements

The concentration of PAs was determined in acid extracts (0.2 N perchloric acid) of the homogenized tissues by reversed-phase HPLC (Merck-Hitachi System) after precolumn derivatization with benzoyl chloride, according to Schenkel *et al*. [24]. The amount of adrenal gland tissue

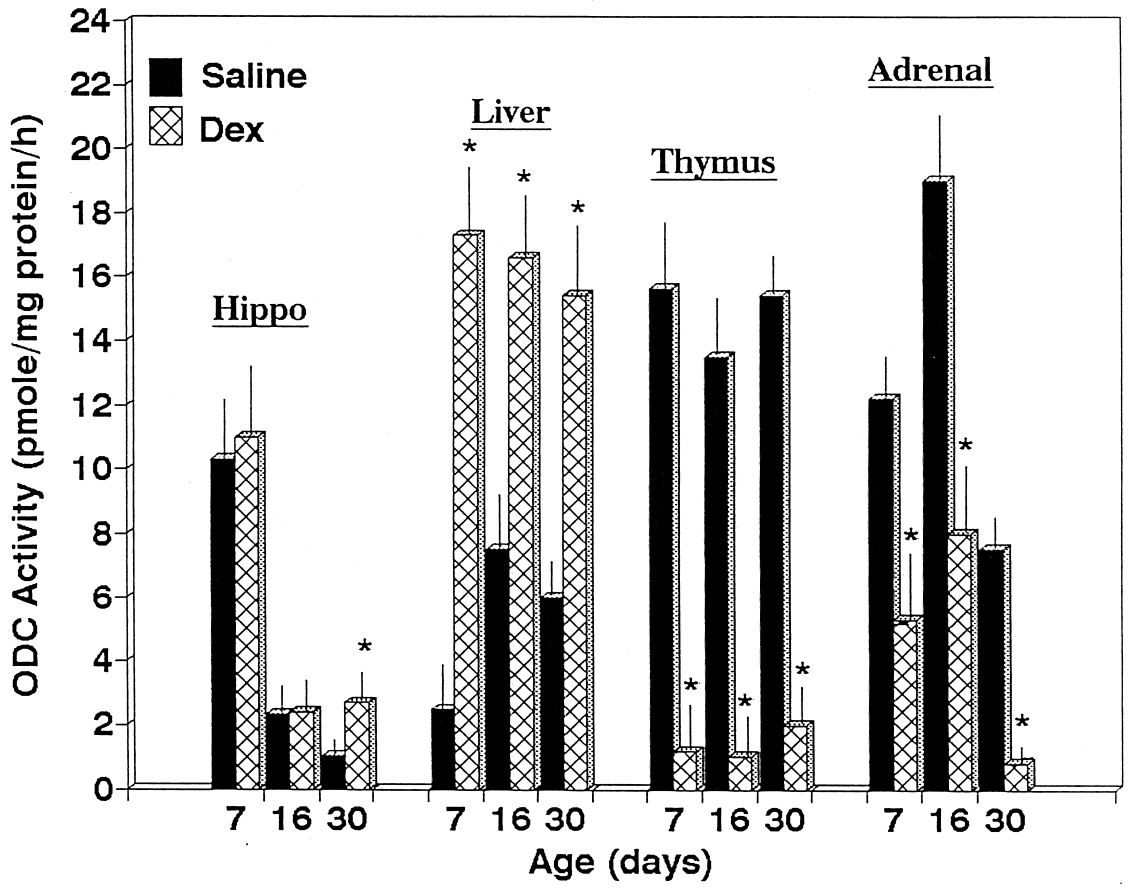

Fig. 1. Effects of a single dexamethasone (Dex, crossed hatched bars) or saline (solid bars) injection at different developmental ages on ODC activity in the hippocampus (Hippo), liver, thymus, and adrenal gland 6 hr after the injection. Results are the mean (± SEM indicated by vertical lines) values of 5 animals. * = $P < 0.01$.

remaining (after ODC aliquot) was insufficient for PA measurements.

2.7. Statistical analysis

ANOVA test followed by non-parametric Tukey's *post hoc* test were performed, and differences considered significant at $P \leq 0.05$. The data were normalized and group differences expressed as percent of control.

3. Results

3.1. The PSR during development

Figure 1 illustrates the postnatal developmental changes in ODC activity and its response to dexamethasone challenge. Confirming our previous findings, ODC activity in the hippocampus decreased (over 10-fold) from its peak at 5–7 days [16] to low-adult levels after day 16. The enzyme activity in the liver increased 2- to 3-fold between 7 and 16 days to reach its high-adult levels at 16 days. In the thymus, the activity was high at day 7 and remained at similarly high levels into adulthood. The enzyme activity in the adrenal gland, which was already high at day 7, increased (by 162%) transiently with a peak at day 16 and declined (by 63%) to adult levels by day 30.

In the hippocampus, the developmental decrease in the concentrations of all PAs paralleled the changes in ODC activity (Table 1), as was previously observed in whole brain [25]. In contrast, putrescine concentrations in the liver and thymus declined during development (Table 1), while ODC activity in these tissues was increased or remained constantly high, respectively (Fig. 1). As illustrated in Fig. 1, the direction of the dexamethasone-induced response in ODC activity persisted throughout development in all peripheral tissues examined. Thus, the increase in liver and the decrease in thymus and adrenal ODC activity were observed at all ages examined in contrast to the hippocampal ODC response, which switched from a period of no change (up to 16 days of age) to the adult pattern of increased activity, as previously observed [16]. While no changes were observed in spermine and spermidine concentrations after dexamethasone, the alterations in ODC activity (Fig. 1) were paralleled by alterations in putrescine concentrations (Table 1).

Table 1
Effects of a single dexamethasone (Dex) or saline injection at different developmental ages on the concentrations of spermine (nmol/mg protein), spermidine (nmol/mg protein), and putrescine (pmol/mg protein) in the hippocampus, liver, and thymus 6 hr after the injection

Age (days)	Hippocampus		Liver		Thymus	
	Saline	Dex	Saline	Dex	Saline	Dex
Spermine						
7	6.4 ± 1.5	7.1 ± 1.8	1.8 ± 0.2	1.4 ± 0.2	3.2 ± 0.4	2.9 ± 0.5
16	3.9 ± 0.6	4.1 ± 0.7	1.9 ± 0.3	2.6 ± 0.4	4.1 ± 0.3	3.4 ± 0.4
30	3.0 ± 0.4	3.0 ± 0.3	3.0 ± 0.4	2.5 ± 0.3	4.4 ± 0.5	4.7 ± 0.5
Spermidine						
7	0.20 ± 0.05	0.17 ± 0.05	0.94 ± 0.23	0.71 ± 0.16	1.10 ± 0.16	0.79 ± 0.15
16	0.05 ± 0.01	0.07 ± 0.02	0.63 ± 0.08	0.79 ± 0.15	1.34 ± 0.23	1.41 ± 0.24
30	0.04 ± 0.01	0.06 ± 0.01	0.55 ± 0.08	0.47 ± 0.07	1.65 ± 0.16	1.96 ± 0.31
Putrescine						
7	158 ± 28	124 ± 24	190 ± 23	268 ± 31*	379 ± 53	267 ± 44*
16	33 ± 13	34 ± 14	91 ± 19	316 ± 38*	207 ± 25	169 ± 19
30	31 ± 13	69 ± 16*	54 ± 13	192 ± 25*	114 ± 15	76 ± 13*

Results are the mean (± SEM) values of 5 animals.
* $P < 0.05$.

3.2. Effects of adrenalectomy on the PSR

Figure 2 illustrates that by 2 weeks after adrenalectomy ODC activity was increased in the hippocampus (161%) and thymus (198%), but decreased (by 49%) in the liver. Restraint stress did not alter the adrenalectomy-induced changes in the liver and thymus, but in the hippocampus of adrenalectomized animals ODC activity was further in-

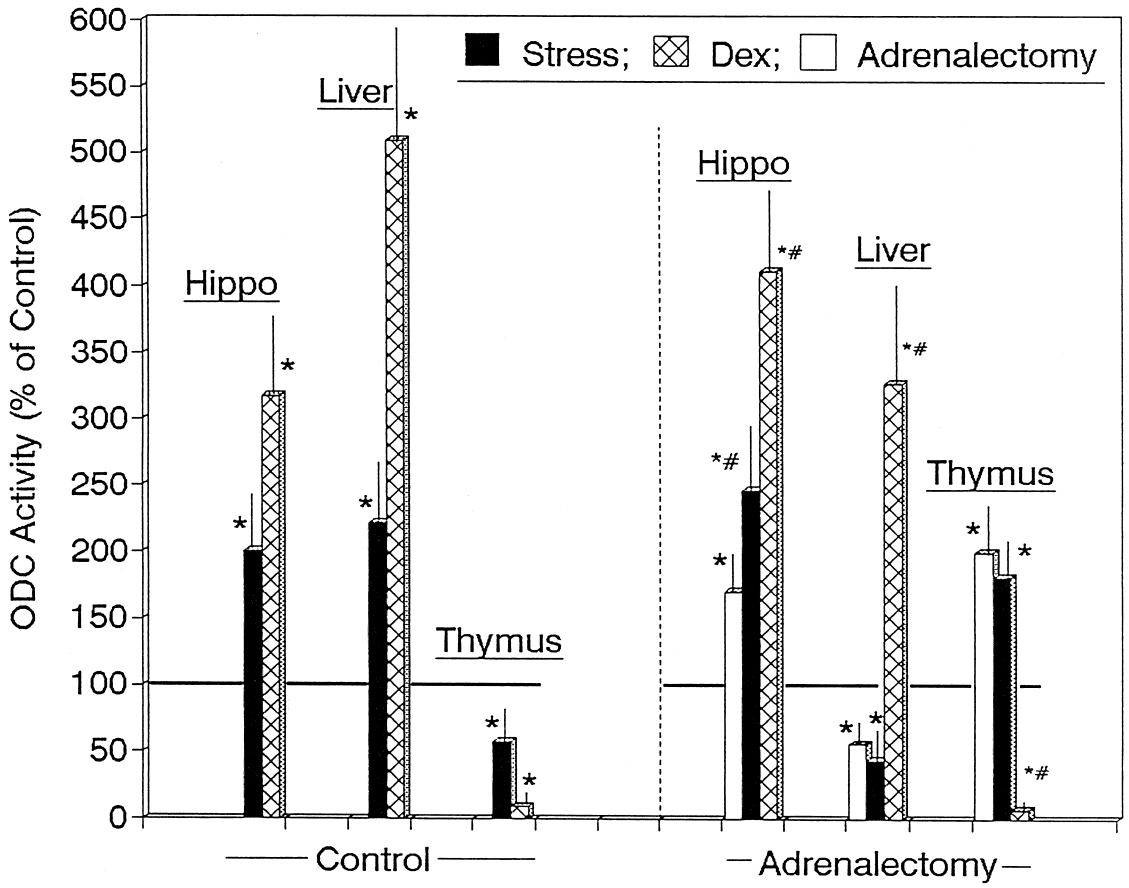

Fig. 2. Effects of adrenalectomy (empty bars) on the response of ODC activity in the hippocampus (Hippo), liver, and thymus to dexamethasone (Dex, crossed hatched bars) or restraint stress (stress, solid bars) treatments. Results are the mean (± SEM indicated by vertical lines) values of 5 animals. *$P < 0.05$, compared to control. #$P < 0.05$, compared to adrenalectomy.

Table 2
Effects of restraint stress or dexamethasone (Dex) treatments of adrenalectomized (AdX) and control rats on spermine (nmol/mg protein), spermidine (nmol/mg protein), and putrescine (pmol/mg protein) concentrations in the hippocampus, liver, and thymus

Group	Hippocampus	Liver	Thymus
Spermine			
Control	3.0 ± 0.3	3.2 ± 0.2	4.9 ± 0.5
Stress	3.8 ± 0.6	3.0 ± 0.3	6.5 ± 0.7
Dex	4.0 ± 0.7	3.5 ± 0.4	5.7 ± 1.4
AdX	5.7 ± 0.2*	3.0 ± 0.4	5.8 ± 1.3
AdX + stress	4.6 ± 0.2*	3.9 ± 0.5	5.4 ± 1.0
AdX + Dex	5.8 ± 0.3*	3.8 ± 0.4	4.4 ± 0.8
Spermidine			
Control	0.047 ± 0.007	0.550 ± 0.080	2.201 ± 0.236
Stress	0.055 ± 0.008	0.393 ± 0.071	2.672 ± 0.393
Dex	0.063 ± 0.016	0.707 ± 0.157	1.951 ± 0.314
AdX	0.033 ± 0.007	0.943 ± 0.236	2.987 ± 0.400
AdX + stress	0.034 ± 0.008	0.708 ± 0.157	3.223 ± 0.550
AdX + Dex	0.039 ± 0.009	0.629 ± 0.177	2.515 ± 0.236
Putrescine			
Control	25.6 ± 8.1	56.6 ± 11.1	102.2 ± 10.2
Stress	46.8 ± 7.3*	93.8 ± 12.5*	66.4 ± 9.3*
Dex	55.5 ± 10.6*	162.9 ± 20.2*	52.1 ± 7.3*
AdX	52.7 ± 12.2*	37.5 ± 10.2	193.5 ± 22.2*
AdX + stress	64.6 ± 17.9*	38.7 ± 11.5	170.3 ± 20.1*
AdX + Dex	86.5 ± 19.5*	139.0 ± 20.5*,**	53.4 ± 10.4*,**

Results are the mean (± SEM) values of 5 animals.
* $P \leq 0.05$, compared to control.
** $P \leq 0.05$, compared to AdX.

creased by the stressor (243%). After dexamethasone treatment, however, similar changes occurred in all tissues of adrenalectomized and control animals (Fig. 2).

Putrescine concentrations were changed in parallel to the changes in ODC activity (Table 2 and Fig. 2). Spermine and spermidine concentrations were not changed in the peripheral tissues, but in the hippocampus, spermine was increased about 2-fold while spermidine remained unchanged (Table 2).

4. Discussion

4.1. Ontogeny of the PSR

The findings indicate that unlike the brain, the direction of the PSR in the peripheral organs presently examined persists throughout postnatal life. Thus, up-regulation of the PSR occurs in the liver, and down-regulation characterizes the response in the thymus and adrenal gland throughout life. This may be the pattern of changes in other peripheral tissues as well [26]. In contrast, the immature brain (up to 16 days of age) does not show the characteristic up-regulation of the adult PSR, but rather a stress non-responsive period is evident.

It appears, therefore, that the switch of the PSR from a stress non-responsive to a stress-responsive mode is unique to the brain. The mechanisms that regulate this developmental switch are intriguing. As we have previously observed [16], the timing of this period appears to correspond to the stress hypo-responsive period in the development of the HPA system, which is characterized by a diminished secretion of corticosteroids in response to stressors [19]. This may indicate that the developmental regulation of the brain PSR is linked to that of the HPA system. In other words, the brain PSR is developmentally regulated, and the switch to the mature pattern corresponds to the cessation of the stress hypo-responsive period in the HPA system.

Interestingly, during the early developmental period, elevated corticosteroids are highly cytotoxic to the brain [27,28], indicating that immature neurons respond differently than mature neurons to glucocorticoid challenge. Glucocorticoids might conceivably cause cellular damage by inhibiting the molecular stress (survival) program, as may be reflected by down-regulation of the proto-oncogenes c-*myc* and *max* [29] in developing neurons that are unable to up-regulate their PSR. As the brain matures, however, acute or short-term (few days) glucocorticoid treatment induces the PSR [11] and may thereby confer a neuroprotective effect. This may explain the observed neuroprotective effect of glucocorticoids against glutamate- and *N*-methyl-D-aspartic acid (NMDA)-induced neurotoxicity [30,31]. It appears then, that the developmental hypo-responsive period of the HPA system to stressors is highly advantageous for survival, as its untimely activation may be detrimental due to glucocorticoid-induced inhibition of biochemical mechanisms essential for cell survival and perhaps coincidental activation of death pathways. However, as the brain matures, stress-induced activation of the HPA system activates the PSR and confers a neuroprotective effect. Interestingly, it has been suggested that persistent increases in ODC activity and putrescine concentration may be contributory factors to nerve cell death after trauma in the mature brain [9]. In contrast, studies with transgenic animals with very high brain ODC activity and putrescine concentrations do not support this notion, but rather indicate that such alterations are neuroprotective [10].

As in the immature brain, down-regulation of the PSR may occur during glucocorticoid-induced apoptosis in embryonic cells [32] and in the thymus [15,33] throughout postnatal life. Dexamethasone-induced down-regulation of ODC activity may indicate negative control of cell viability by glucocorticoids in the adrenal gland as well; this would be in contrast to the up-regulation of PA metabolism and positive control of cell viability induced by adrenocorticotropic hormone (corticotropin, ACTH) in the adrenal gland [34]. Perhaps, inability to *transiently* up-regulate PA metabolism may be a universal indicator of susceptibility to cell death.

Our previous observations indicate that the ontogenesis of the PSR in the brain is region-specific [16]. Thus, the developmental switch of the PSR appears to occur later in the hippocampus than in the striatum [16], a region known

to mature earlier than the hippocampus [35], indicating that the PSR depends on the stage of neuronal maturation. This implies that both when planning future studies and interpretating previous data, regional differences in the intensity of the PSR would reflect true functional differences between neuronal populations only after the period of early development is over.

Of interest is the observation that the period of the developmental switch in the PSR, which occurs somewhere between 16 and 30 days of age, coincides with the period of endocrine and sexual maturation in rats. In human, the corresponding period is associated with a high incidence of affective disorders [17]. It is important, therefore, to further elucidate the mechanisms that control this developmental switch. Furthermore, in light of our previous observations that the brain ODC activity, in contrast to the periphery, can be blocked by a long-term, but not short-term, treatment with lithium [11,12], it would be important to determine the effect of lithium treatment on the PSR during development.

4.2. The role of adrenal stress hormones in activating the PSR

In the peripheral organs studied, the PSR appears to be dependent only on stress-induced activation of the HPA axis and on increased circulating glucocorticoid concentrations rather than on neuronal activation. However, in the adult brain, the PSR can be induced independently by increased circulating glucocorticoids or by direct activation of the neuronal circuitry.

As during development, the PSR in adults, characterized in the present study at 6 hr after the stress challenge, is composed of parallel changes in ODC activity and in putrescine concentrations without associated changes in spermine and spermidine. Adrenalectomy itself resulted 2 weeks later in increased ODC activity and putrescine concentrations in the hippocampus and thymus, but a decrease in ODC activity was noted in the liver. While spermine and spermidine concentrations remained unchanged in the peripheral tissues, adrenalectomy led to an increase in spermine (but not spermidine) in the hippocampus. This exceptional increase in spermine concentrations in the hippocampus may reflect activation of the cellular stress program in response to glucocorticoid depletion after adrenalectomy, a treatment known to lead to delayed nerve cell death in the hippocampal dentate gyrus [36,37]. In the thymus, despite the lack of increase in PA (spermine and spermidine) concentrations, the elevation in ODC/putrescine may reflect enhanced cell survival in this organ after adrenalectomy.

Lastly, it is important to point out that the measurements performed in the present set of studies indicate static changes in total tissue PAs, but alterations in PA turnover are certainly possible and should be examined. Furthermore, it should be emphasized that we measured changes in ODC activity only at a single time point after the stress challenge. Alterations in the temporal profile of stress-induced changes (e.g. between 1 and 24 hr after the stress or dexamethasone challenge) are possible and should be determined in future studies.

Taken together, the results warrant the following conclusions: i) Unlike peripheral organs, the brain PSR is developmentally regulated and its ontogenesis is brain region-selective, indicating dependence on the stage of neuronal maturation; ii) The developmental switch to a mature brain PSR pattern corresponds in time to the cessation of the stress hypo-responsive period in the HPA system; iii) In the periphery, the PSR appears to be dependent principally on stress-induced activation of the HPA axis and on increased circulating glucocorticoid concentrations rather then on neuronal activation; iv) In the brain, the PSR can be induced independently by increasing circulating glucocorticoids or by direct activation of the neuronal circuitry (i.e. neurogenic activation); and v) Up-regulation of the PSR, as in the mature brain and liver, appears to be constructive and may be implicated in cell survival, while its down-regulation, as in the thymus and adrenal gland and during early brain development, may be implicated in cell death.

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