



# PSA-NCAM: an important regulator of hippocampal plasticity

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## Abstract

The Neural Cell Adhesion Molecule (NCAM) serves as a temporally and spatially regulated modulator of a variety of cell-cell interactions. This review summarizes recent results of studies aimed at understanding its regulation of expression and biological function, thereby focussing on its polysialylated isoforms (PSA-NCAM). The detailed analysis of the expression of PSA and NCAM in the hippocampal mossy fiber system and the morphological consequences of PSA-NCAM deficiency in mice support the notion that the levels of expression of NCAM are important not only for the regulation and maintenance of structural changes, such as migration, axonal growth and fasciculation, but also for activity-induced plasticity. There is evidence that PSA-NCAM can specifically contribute to a presynaptic form of plasticity, namely long-term potentiation at hippocampal mossy fiber synapses. This is consistent with previous observations that NCAM-deficient mice show deficits in spatial learning and exploratory behavior. Furthermore, our data points to an important role of the hypothalamic–pituitary–adrenal axis, which is the principle adaptive response of the organism to environmental challenges, in the control of PSA-NCAM expression in the hippocampal formation. In particular, we evidence an inhibitory influence of corticosterone on PSA-NCAM expression. © 2000 Published by Elsevier Science Ltd on behalf of ISDN. All rights reserved.

## 1. Introduction

The Neural Cell Adhesion Molecule (NCAM), a member of the immunoglobulin (Ig) superfamily, is probably the most widely studied adhesion molecule to date due to its implication in a variety of cell–cell and/or cell–substrate interactions via homophilic and heterophilic mechanisms. Alternative splicing of a single-copy gene yields a variety of isoforms, which differ in their protein backbone or their mode of attachment to the plasma membrane.

Further variability among NCAMs is generated at the post-translational level. Long homopolymers of  $\alpha$ -2-8-linked sialic acid residues, generally referred to as PSA, constitute up to 30% of the highly sialylated

NCAM isoforms, known under the general term of PSA-NCAM. This, for vertebrates, unusual carbohydrate polymer is thought to decrease homophilic binding and thereby to attenuate cell adhesion [1]. Several studies are consistent with a direct effect on NCAM-mediated adhesion, as for example, the presence of PSA decreases the binding between NCAM-bearing liposomes [1]. PSA is also thought to affect the relative degree of overall membrane-membrane apposition between cells [2]. These and other studies on a variety of cell-cell interactions have led to the hypothesis that PSA could also affect other molecules not directly involved in NCAM-mediated adhesion [1,3]. Recently, evidence for a positive role of PSA-NCAM in the regulation and promotion of axon growth and fasciculation [4,5] as well as cell migration processes [6] have been provided.

In any case, PSA on NCAM is a potent regula-

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tor of cell interactions involving membrane contact [2] reviewed in [7–9]. Its presence on cell surface seems to permit cells or axons to interact with their neighbors, thereby allowing them to respond to guidance or targeting cues, which are essential for the development and function of the nervous system. The spatio-temporal pattern of PSA-NCAM expression during development correlates well with such a role. Furthermore, its expression in discrete areas that keep the ability to undergo structural and functional changes in the adult central nervous system also argues for an important function of PSA-NCAM in the maintenance of plasticity in the mature brain [10,11]. One such a site, where prominent expression of PSA-NCAM has been associated with the maturation and differentiation of newly born neurons, is the rodent hippocampal formation [12–14], a structure which has been implicated in learning and memory processes [15].

A possible link between NCAM-mediated interactions and cognitive functions has been suggested by a variety of experiments: (i) administration of anti-NCAM antibodies induces amnesia in rats [16] and interferes with the consolidation of memory in chickens [17]; (ii) injection of anti-NCAM antibodies into the CA1 region in rat inhibits subsequent long-term potentiation-induction (LTP) [18,19]; (iii) NCAM deficient mice show deficits in spatial learning when tested in the Morris water maze [20]. Polysialylation of NCAM has also been involved in memory since: (i) PSA-NCAM is transiently increased as a consequence of learning processes [21,22]; (ii) administration of endoneuraminidase NE (endoN), an enzyme which removes PSA by cleaving 2–8 linked polysialic acid, diminishes performance in a water maze [23]; (iii) treatment of hippocampal slices with endoN block the induction of LTP in the CA1 sub-field [23,24].

Moreover, the hippocampal formation is the main cerebral target site of glucocorticoids action. These hormones are secreted in the periphery by the adrenal glands and have a wide array of effects throughout the body (for review see [25]). Secretion of corticosterone, the major glucocorticoid in rats, is increased in response to stress and facilitates the physiological responses necessary to cope with the situation of emergency. It modulates cognitive functions and LTP following an inverted U-shaped curve, and a dysregulation of the activity of the hypothalamo-pituitary-adrenal (HPA) axis induces cognitive deficits and alterations in LTP (for review see [26]). Beside these effects, corticosterone has a major influence on structural plasticity in the hippocampal formation (for review see [27]). For example, suppression of corticosterone, obtained by adrenalectomy, increases neurogenesis within the dentate gyrus [28]. In contrast, high

levels of the hormone (induced via exogenous administration or stress) decrease neurogenesis in the same structure [29,30].

Here we review recent data on the role of PSA-NCAM in the development and function of the hippocampal system, which have been acquired using two paradigms: (i) the genetic inactivation of the NCAM-gene to generate mice lacking NCAM and PSA; (ii) the use of animal models differing in their level of corticosterone secretion.

## 2. Genetic analysis of PSA-NCAM function

### 2.1. Deficits in axonal growth and fasciculation in the hippocampal formation of NCAM-deficient mice

PSA is strongly expressed in subpopulations of granule cells in the dentate gyrus and their axonal projections, the mossy fibers (mfs). Each granule cell grows a single axon, which forms en passant synapses with the proximal dendrites of the pyramidal cells in the CA3 region of the hippocampus. We used Timm's staining, which specifically reveals mfs and most prominently their synaptic expansions, to study their deposition in PSA-NCAM deficient (KO) and control mice. Wild-type (WT) and heterozygous animals show a strong and homogeneous staining of the mossy fiber pathway. In the CA3 region, the mfs are mainly confined to the suprapyramidal tract, i.e. the apical dendritic region of the pyramidal cells, forming the well-distinguished stratum lucidum (Fig. 1a). Only in the region close to the hilus do the mfs cross the pyramidal cell layer. Furthermore, most of the mfs appear to reach the CA3-CA2 border. In contrast, adult NCAM-/- animals show a 20% reduction in staining intensity and striking alterations in the distribution of mfs and their terminals, indicated by the invasion of the pyramidal cell layer and a loss of the laminated appearance of the structure (Fig. 1b).

These observations have been confirmed using the Golgi technique, where we observed that the restricted distribution of thorny excrescences, representing the post-synaptic parts of mf-terminals, is altered in the absence of PSA-NCAM. While in the wild-type (Fig. 1c), all terminals are restricted to a well-defined band, in the mutant (Fig. 1d) they appear dispersed over a far larger area of the dendrite, including the pyramidal cell layer itself. In addition, immunohistochemistry in association with confocal microscopy as well as electron microscopy revealed that a total loss of fasciculation of the mf-axons underlies the morphological alterations as indicated by the Timms and Golgi methods [4]. In turn, these appear to induce the abnormal positioning of mf-terminals on CA3 neur-

ons. Nevertheless, morphologically the ectopically formed synapses appear normal in form and size [5].

## 2.2. Long-term plasticity requires NCAM molecules at mossy fiber synapses

To investigate the electrophysiological properties of mf-synapses, we first addressed the question of whether lack of NCAM shows consequences on transmitter release. Frequency facilitation, a form of short-term synaptic plasticity, occurs as a consequence of a change in the frequency of stimulation and results in a reversible increase of the mfs response. This phenomenon was unaffected in the knockout mouse compared to the wild-type, since for both group of animals, increasing the frequency of stimulation resulted in a comparable increase in the size of the mf response. Furthermore, it has been shown that a synapse activated twice at short intervals, shows a stronger response to the second stimulus due to augmented transmitter release. This process is referred to as paired-pulse facilitation (PPF). As for frequency facilitation we found no differences in this process between control and mutant animals. Since these two forms of plasticity depend upon the probability of transmitter release, we concluded from this first set of experiments that NCAM-deficient mice do not have markedly altered probability of glutamate release, suggesting that basic synaptic transmission parameters are unaffected in the absence of NCAM and PSA.

In a second step we aimed to investigate the role of NCAM in long term potentiation (LTP). In wild-type

mice tetanic stimulation elicited a robust mossy fiber LTP which lasted over the analyzed interval. In contrast, only weak LTP was observed in NCAM-deficient mice when measured one hour after induction (Fig. 2). The potentiation immediately after the tetanus, however, was not significantly altered in the knockout mice suggesting a crucial role of NCAM in late but not early phases of LTP.

## 3. Hormonal regulation of PSA-NCAM expression

### 3.1. Influence of corticosterone in young adult rats

We studied the functional correlation between PSA-NCAM expression, neurogenesis and corticosterone levels by manipulating the levels of the hormone in 2 month-old rats. Suppression of corticosterone secretion by adrenalectomy (Adx) increased the expression of PSA (Fig. 3), but not NCAM [31], in the dentate gyrus. In parallel, we found an enhancement of neurogenesis in this structure. These effects were specific to the dentate gyrus since neither the density of PSA-NCAM-immunoreactive (IR) cells in the piriform cortex or proliferation in the subependymal layer were influenced by Adx [31].

In parallel, we investigated whether the effects of Adx on PSA-NCAM expression and neurogenesis could be blocked by the restitution of corticosterone levels. Since corticosterone secretion follows a circadian rhythm (levels of the hormone are low during the day and rise during the night), we mimicked the differ-

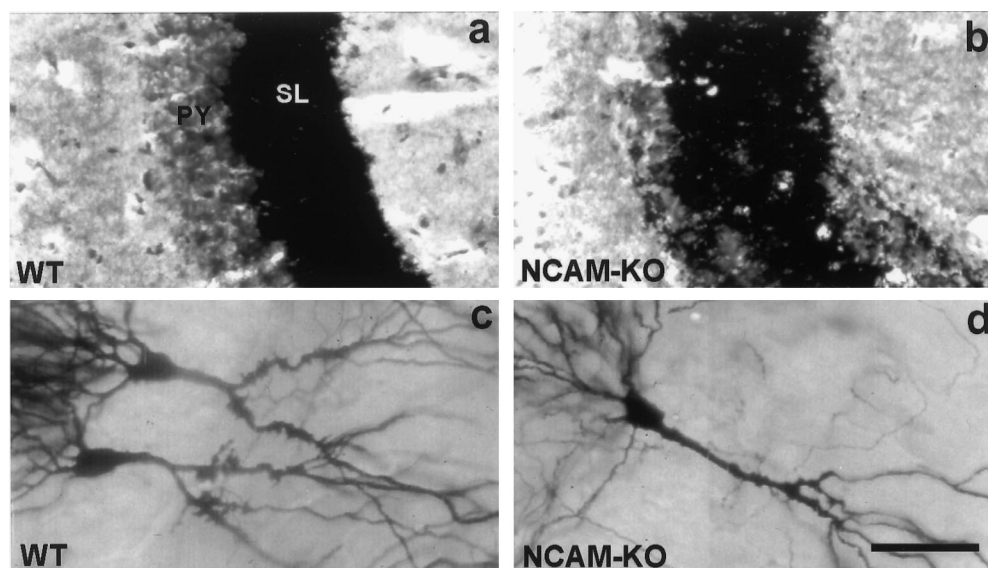


Fig. 1. Analysis of mossy fiber tracts in adult wildtype (WT) and NCAM-deficient (KO) mice. (a) and (b) Timms staining reveals the loss of lamination of the mutant CA3 region. Labeling is found between the pyramidal neurons, indicating the existence of mf-terminals in this region. (c) and (d) Golgi staining of CA3 pyramidal neurons. Notice the broader distribution of thorny excrescences on the apical dendrites of the cells compared to their restricted appearance in the wildtype situation. PY, pyramidal cell layer. SL, stratum lucidum. Bar: 75 mm in (a) and (b); 80  $\mu$ m in (c) and (d). Reprinted from Cremer et al. [4].

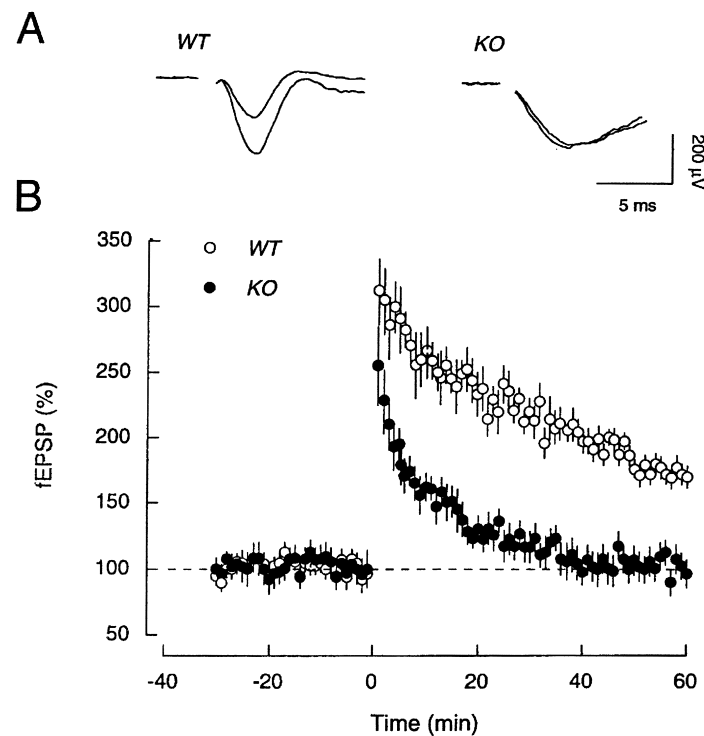


Fig. 2. Mossy fiber long-term potentiation is reduced in PSA-NCAM deficient mice. (A) Superimposed sample field potential recordings before and 55–60 min after tetanization in wild-type (WT) and knock-out (KO) animals. (B) Mossy fiber field potentials plotted against time. After baseline responses were stable for at least 30 min a tetanus was given to induce LTP. From Cremer et al. [5].

ent phases of corticosterone secretion [32]. Diurnal levels were simulated by the restitution of constant low levels of the hormone. Nocturnal levels were obtained by adding corticosterone during the night. To restore

the circadian fluctuation, the two previous treatments were combined. We found that for the normalization of PSA-NCAM expression simulation of the complete circadian fluctuation was essential. In contrast, low

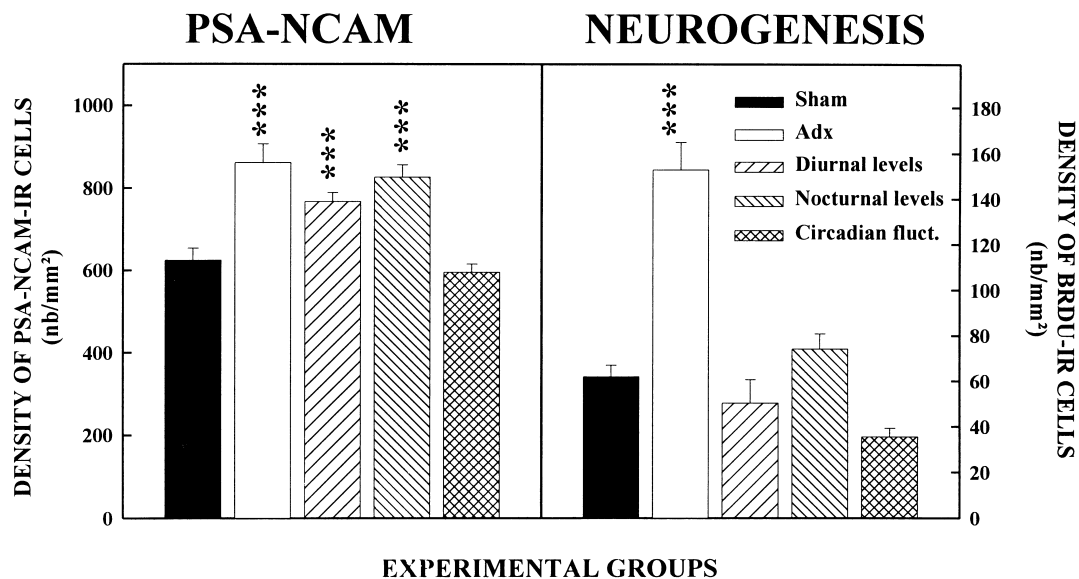


Fig. 3. Influence of different substitutive treatments of corticosterone on the expression of PSA-NCAM and neurogenesis within the dentate gyrus. Reprinted from Rodriguez et al. [31] with permission of BlackScience. \*\*\* $P < 0.001$  in comparison with the other experimental groups.

but constant levels of the hormone were sufficient to prevent an increase in neurogenesis (Fig. 3).

### 3.2. Influence of aging

#### 3.2.1. PSA-NCAM expression and cognitive capacity

Aging is accompanied by a decline in cognitive functions. Among a population of aged rats, the extent of memory dysfunction has been related to the magnitude of changes occurring in the hippocampal formation, the brain region that appears most vulnerable to aging [33–35]. It has been suggested that the excessive release of corticosterone is responsible for the alterations in brain function observed during aging (for review see [36]) since: (i) aging is accompanied by an increase in basal levels of circulating corticosterone which has been correlated with the extent of memory deficits in aged rats [37]; (ii) adrenalectomy in middle-aged rats protects hippocampal cells from naturally occurring death and improves cognitive function in the aged animal [38]; (iii) handling of neonatal rats, which has been shown to prevent age-related increase in corticosterone, postpones cognitive deficits [39]; (iv) long term treatment of middle-aged rats with corticosterone accelerates brain aging [40]; (v) prenatal stress, which has been shown to increase corticosterone levels, accelerates the appearance of age-related cognitive deficits [41].

As shown (Fig. 3), corticosterone inhibits PSA-NCAM expression in the dentate gyrus in young animals. Thus, a decline in its expression could be expected in aged rats showing naturally increased levels of corticosterone. Indeed, such a decline was

described in the dentate gyrus of 24-month old animals (Fig. 4) [42,43]. To investigate the functional significance of the PSA-NCAM decline during aging, we took advantage of the inter-individual differences as a natural model of structure-function studies. Indeed, among a population of aged rats, not all animals exhibit cognitive deficits when tested in spatial learning paradigms [33–35]. In order to investigate whether age-dependent changes in expression of PSA-NCAM were accentuated in aged rats with learning impairments, 7-months old and 24-months old rats were assessed for their cognitive abilities using a Morris water maze. While 7 month-old rats showed no major variance in learning abilities, 24 month-old animals could be subdivided into two groups: aged unimpaired (AU) and aged impaired (AI; Fig. 4). Both groups of aged animals showed a comparable decline in PSA-NCAM-IR cells in the dentate gyrus and the piriform cortex. A correlation with spatial learning capabilities could not be found indicating that these cognitive deficits are not related to PSA-NCAM expression.

#### 3.2.2. Manipulation of corticosterone levels

The decrease of PSA-NCAM during aging shown above could result from: i) a loss of cells normally expressing PSA-NCAM; (ii) a down-regulation of the machinery responsible for the biosynthesis and attachment of PSA to NCAM; (iii) a decline in neurogenesis [43,45]; (iv) an age-related increase in the levels of circulating corticosterone [36]. We examined this last hypothesis and investigated whether the effect of aging on PSA-NCAM expression and neurogenesis could be reversed by suppression of corticosterone levels. In a

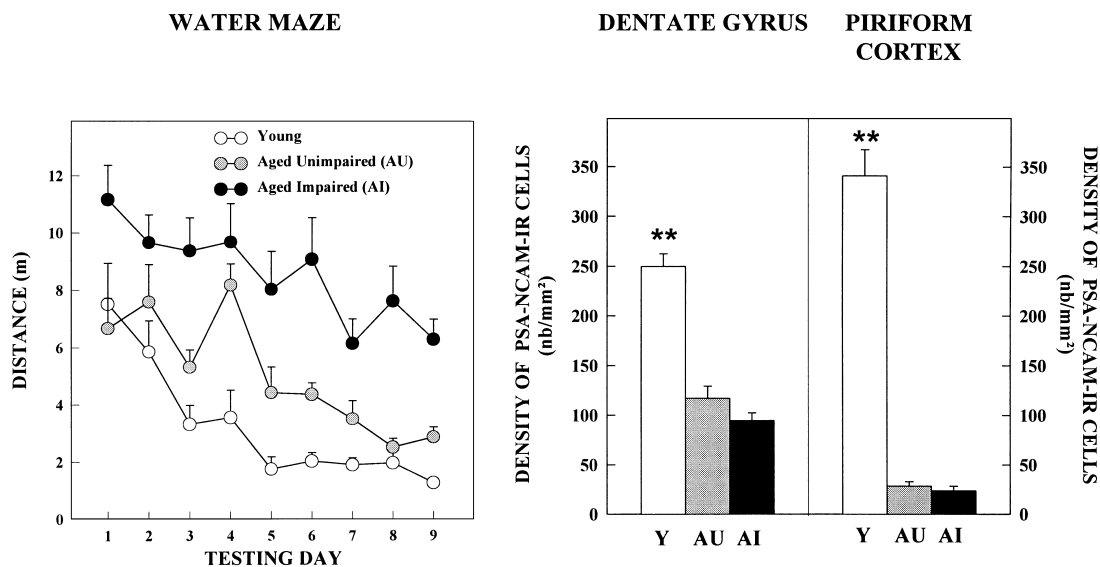


Fig. 4. Spatial learning in a water maze and PSA-NCAM-IR cells within the dentate gyrus and the piriform cortex of young (7 months) and aged (24 months) rats. Behavioral data and PSA-NCAM expression within the dentate gyrus are reprinted from Abrous et al. [44] with permission of Elsevier Science. \*\* $P < 0.01$  in comparison with the aged groups.

first step, adrenalectomy was performed in 24-month old rats. A subgroup of these animals received a treatment aimed to restore the complete circadian rhythm of the hormone (see Fig. 3). We found that PSA-NCAM expression remained unchanged relative to controls whereas neurogenesis was stimulated through a glucocorticoid-specific mechanism [46]. In a second step, we studied whether loss of PSA-NCAM could be prevented by intervening earlier in life. We show that adrenalectomy performed in middle-aged rats (12-month-old rats) does not prevent downregulation of PSA-NCAM expression when measured at 24-months of age (Fig. 5). In contrast, cell proliferation was maintained in the Adx group.

#### 4. Conclusions

The analysis of the hippocampal formation of genetically modified mice entirely devoid of NCAM and PSA reveals the important function of the molecules in the development, function and plasticity of this structure. Mfs in PSA-NCAM deficient mice show almost no signs of fasciculation during their course through the CA3 region. Furthermore, we have been able to demonstrate that PSA-NCAM is essential for the correct establishment of synaptic connectivity. In mutants, mf-terminals form within the pyramidal cell layer, thereby destroying its normal laminated organization. The observation that both these defects are more severe in adult than in young animals suggests an essential role for the molecule in the maintenance of structural plasticity in the mature nervous system. We provide the first genetic proof for a vertebrate cell adhesion molecule playing a key role in axonal growth and pathfinding.

The investigation of synaptic plasticity in the mf-

pathway of mutants revealed a further specific role of PSA-NCAM in the hippocampus. Indeed, electrophysiological analysis revealed a key function of PSA-NCAM in long-term potentiation in the absence of alterations in basic synaptic transmission and short-term plasticity. At the moment we are unable to discriminate if the altered synaptic properties are due to the ectopic position of the terminals on the cell bodies and proximal dendrites of the pyramidal neurons, or if PSA-NCAM serves a direct function in mf LTP. The generation of animals in which the ablation of NCAM and/or PSA can be induced in a conditional manner will be required to answer this question.

The second part of the work presented here concerns the influence of epigenetic factors influencing PSA-NCAM expression and its possible link to neurogenesis permanently occurring in the dentate gyrus. We demonstrated that a hormone secreted in the periphery, corticosterone, is involved in the regulation of PSA-NCAM in the central nervous system. Since NCAM expression was unaffected by adrenalectomy, an alteration of the biosynthesis and attachment of PSA to NCAM might be involved in the up-regulation of PSA-NCAM expression. Thus corticosterone, which is known to act, like other steroid hormones, at the level of gene transcription, could exert its control over PSA-NCAM expression by modulating the expression of the polysialyltransferases PST I or STX, the key enzymes involved in NCAM polysialylation [7]. It has been shown that corticosterone acts on two types of receptors, both present in the dentate gyrus: type I receptors which have a high affinity for corticosterone whereas type II receptors have a low affinity for the hormone [47]. Our data suggest that stimulation of the type I receptor may be sufficient to mediate the effects of the corticosterone on neurogenesis whilst its influence on PSA-NCAM depends on type II receptors.

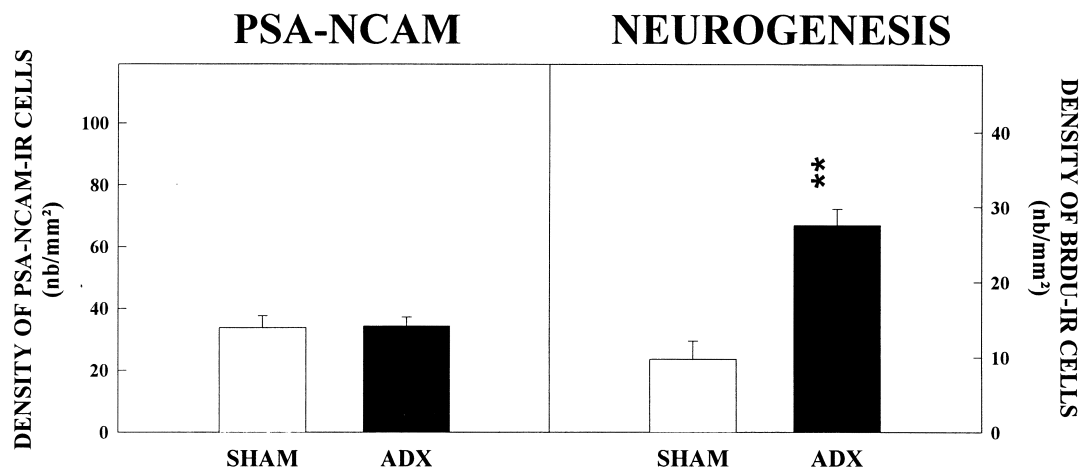


Fig. 5. Effects of adrenalectomy in middle-aged rats on PSA-NCAM expression and neurogenesis measured in the dentate gyrus at 24 months of age. \*\* $P < 0.01$  compared with the sham group.

This is indicative of a functional decoupling of PSA-NCAM expression and neurogenesis. NCAM and corticosterone have been shown to inhibit astrocyte proliferation and it has been suggested that anti-proliferative properties of NCAM may be mediated by glucocorticoid receptors pathway [48]. Although it has been shown by others [28,29] and by us [46] that the newly born cells were mainly neurons, it cannot be excluded that a similar mechanism occurred in neuronal progenitors. In other words, corticosterone and NCAM may inhibit proliferation of neuronal precursors by a common pathway.

Aging is accompanied by a decline in neurogenesis and PSA-NCAM expression in the dentate gyrus. Our analysis of the influence of corticosterone on neurogenesis and PSA-NCAM expression in aged rats allows three conclusions: (i) in the aged dentate gyrus, stem cells are still present and able to re-enter the cell cycle; (ii) the decline in neurogenesis in aged animals results from the action of the inhibitory factor corticosterone; (iii) the loss of PSA-NCAM during aging is not related to a decrease in neurogenesis or to an excessive release of circulating corticosterone.

Altogether, the data presented here points to the important role of PSA-NCAM during development and in the maintenance of plasticity in the aging nervous system. Thus, understanding the function and regulation of this molecule represents a fundamental prerequisite for the development of therapies in order to maintain plasticity throughout life and functional recovery after brain damage.

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