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PSA-NCAM expression in the human prefrontal cortex

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Abstract

The prefrontal cortex (PFC) of adult rodents is capable of undergoing neuronal remodeling and neuroimaging studies in humans have revealed that the structure of this region also appears affected in different psychiatric disorders. However, the cellular mechanisms underlying this plasticity are still unclear. The polysialylated form of the neural cell adhesion molecule (PSA-NCAM) may mediate these structural changes through its anti-adhesive properties. PSA-NCAM participates in neurite outgrowth and synaptogenesis and changes in its expression occur parallel to neuronal remodeling in certain regions of the adult brain. PSA-NCAM is expressed in the hippocampus and temporal cortex of adult humans, but it has not been studied in the PFC. Employing immunohistochemistry on sections from the rostromedial superior frontal gyrus we have found that PSA-NCAM is expressed in the human PFC neuropil following a laminated pattern and in a subpopulation of mature neurons, which lack doublecortin expression. Most of these cells have been identified as interneurons expressing calbindin. The expression of PSA-NCAM in the human PFC is similar to that of rodents. Since this molecule has been linked to the neuronal remodeling found in experimental models of depression, it may also participate in the structural plasticity described in the PFC of depressed patients.

Keywords: Structural plasticity; Depression; Interneuron

1. Introduction

Neurons in the adult brain are able to modify their structure undergoing changes in their dendritic arborization, remodeling of spines and synaptic reorganization. These plastic phenomena are triggered in certain physiological conditions, underlie basic cognitive phenomena and are particularly evident when elicited as a response to aversive experiences. The prefrontal cortex (PFC) is one of the areas of the adult brain known to display neuronal structural plasticity. Dendritic and spine remodeling has been observed in the medial PFC of rodents after chronic stress (Cook and Wellman, 2004; Radley et al., 2004, 2005), chronic corticosterone treatment (Wellman, 2001) or changes in blood pressure (Vega et al., 2004). Moreover, neuroimaging data in human patients also indicates that major depression and other psychiatric conditions, such as schizophrenia or bipolar disorder, are accompanied by structural changes in this cortical region (Drevets, 2001; Ongur et al., 1998; Rajkowska et al., 1999).

Structural changes in neurons are likely to be mediated by the expression of cytoskeletal proteins and cell adhesion molecules. One of the molecules that has received more attention in the recent years is the polysialylated form of the neural cell adhesion molecule (PSA-NCAM). The membrane protein NCAM can incorporate long chains of PSA, which confer it anti-adhesive properties (Rutishauser and Landmesser, 1996). Consequently, the expression of PSA-NCAM allows neurons to participate in plastic events such as neurite outgrowth (Zhang et al., 1992) or synaptic reorganization (Seki and Rutishauser, 1998). In adult animals, this molecule is expressed in cerebral regions that are undergoing continuous structural plasticity, such as the hypothalamo-neurohypophyseal system (Theodosis et al., 1994), the olfactory bulb (Miragall et al., 1988), the piriform and entorhinal cortices (Seki and Arai, 1991a), the amygdala (Nacher et al., 2002b) and the hippocampus (Seki and Arai, 1991b). Changes in the levels of expression of this molecule accompany the structural reorganization induced by chronic stress in the hippocampus

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and the amygdala (Cordero et al., 2005; Pham et al., 2003). We have recently shown that the medial PFC of adult rats also displays high levels of PSA-NCAM expression, which is present both in the neuropil and in neuronal somata, mostly in interneurons expressing calbindin D-28k, somatostatin and neuropeptide Y (Varea et al., 2005). The presence of PSA-NCAM in some regions of the adult human brain has already been reported (dentate gyrus, Mikkonen et al., 1999; Ni Dhuill et al., 1999, temporal cortex, Arellano et al., 2002), but there are no data available on its expression in the PFC. In order to test whether this molecule is present in the human PFC and to identify the phenotype of the cellular elements expressing it, we have analyzed PSA-NCAM expression using immunohistochemistry and we have combined it with the analysis of specific markers for neurons, glial cells or subtypes of interneurons in the rostromedial part of the superior frontal gyrus of the dorsolateral prefrontal cortex of adult humans (Brodmann area 9). This area has been selected because, at least some regions of the rat medial PFC, present anatomical and functional dorsolateral-like features (Uylings et al., 2003). We have also analyzed the expression of doublecortin (DCX), a neuronal specific protein involved in microtubule dynamics, which participates in plastic phenomena such as cell migration or neurite outgrowth (Gleeson et al., 1999; Shmueli et al., 2001) and it is considered a reliable marker of recently generated neurons in the adult hippocampus (Brown et al., 2003).

2. Experimental procedures

2.1. Human samples

Human frozen samples from the rostromedial part of the superior frontal gyrus (dorsolateral prefrontal cortex, Brodmann area 9) were obtained from the Neurological Tissues Bank of the University of Barcelona. Samples were obtained from five subjects without any neurological abnormality, the average age was 59.6 years (42–74) and the time post-mortem before freezing the samples was 8.5 h (3.5–17.5). The tissue was unfrozen and fixed by immersion in a solution of paraformaldehyde 2.5% in a lysine-phosphate buffer, pH 7.4 for 12 h. The lysine-phosphate buffer was prepared 1:1 from a solution of PB 0.1 M pH 7.4 and a solution 0.2 M of lysine adjusted to pH 7.4 using a solution of Na_2HPO_4 0.1 M. The buffer is mixed with a concentrated solution of paraformaldehyde 3:1 and 0.214 g of sodium peryodate is added for each 100 ml just before use. After fixation, samples were washed using PB and 50 μm sections were obtained using a vibratome. Sections were then postfixed in the same solution for 20 min. After fixation, sections were washed in PB pH 7.4 and maintained in PB with sodium azide 0.05% until used.

2.2. PSA-NCAM immunohistochemistry

Tissue was processed ''free-floating'' for immunohistochemistry as follows. Briefly, sections were incubated for 1 min in an antigen unmasking solution (0.01 M citrate buffer, pH 6) at 100 °C. After cooling down the sections to room temperature they were incubated with 10% methanol, 3% H_2O_2 in phosphate buffered saline (PBS) for 10 min to block endogenous peroxidase activity. After this, sections were treated for 1 h with 5% normal donkey serum (NDS) (Jackson Laboratories) in PBS with 0.2% Triton-X100 (Sigma) and were incubated overnight at room temperature in mouse monoclonal Men-B anti-PSA-NCAM antibody (1:1400; Abcys). After washing, sections were incubated for 30 min with donkey anti-mouse IgM biotinylated antibody (Jackson Laboratories, 1:250), followed by an avidin-biotin-peroxidase complex (ABC, Vector Laboratories) for 30 min in PBS. Color development was achieved by incubating with 3,3′ diaminobenzidine tetrahydrochloride (DAB, Sigma) for 4 min. PBS containing 0.2% Triton-X100 and 3% NDS was used for primary and secondary antibodies dilution.

Pretreatment of the PSA-NCAM antibody with α-2,8-linked sialic polymer (colominic acid, Sigma) overnight, or the primary antibody omission during the immunohistochemistry prevented all the labeling in the human mPFC.

2.3. Double immunofluorescence

In order to characterize the phenotype of PSA-NCAM immunoreactive cells, we have performed double immunohistochemistry using an anti-PSA-NCAM antibody and antibodies against different neuronal, astroglial and oligodendroglial markers. In general, sections were processed as described above, but the endogenous peroxidase block was omitted. The sections were incubated overnight with mouse monoclonal IgM anti-PSA-NCAM antibody (Men-B, 1.1400) and one of the following primary IgG antibodies: monoclonal mouse anti-Neuronal nuclear antigen (NeuN, Chemicon Int.; 1:100); polyclonal rabbit anti-glial fibrillar acidic protein (GFAP, Sigma 1:500), monoclonal mouse anti-glutamate decarboxylase (GAD67, Chemicon Int; 1:1000); monoclonal mouse rip antibody (Developmental Studies Hybridoma Bank, 1:1000); polyclonal rabbit anti-calbindin-D28K (SWANT, 1:2000); polyclonal rabbit anti-calretinin (SWANT, 1:2500); polyclonal rabbit anti-parvalbumin (SWANT, 1:2000); polyclonal rabbit anti-vasoactive intestinal peptide (VIP, kindly provided by Dr. T.J. Görcs, 1:1000) (Lantos et al., 1995); polyclonal rabbit anti-neuropeptide Y (NPY, kindly provided by Dr. T.J. Görcs, 1:1000) (Csiffary et al., 1990); polyclonal rabbit anti-somatostatin (SST, kindly provided by Dr. T.J. Görcs, 1:200) (Leranth and Frotscher, 1987); monoclonal mouse anti-cholecystokinin (CCK, CURE, 1:1000). After washing, sections were incubated with donkey anti-mouse IgM, donkey anti-mouse IgG or donkey anti-rabbit IgG secondary antibodies conjugated with Alexa 488 or Alexa 555 (Molecular Probes, 1:200) in PBS containing 0.2% Triton X-100 and 3% NDS. In order to reduce the unspecific autofluorescence, we have followed a previously described protocol (Schnell et al., 1999). In brief, after immunohistochemistry sections were washed with distilled water and incubated for 25 min in the darkness with a solution containing ammonium acetate 50 mM and cupric sulphate 10 mM (pH adjusted to 5 using diluted HCl). After incubation sections were washed with distilled water and PBS.

2.4. Quantitative analysis

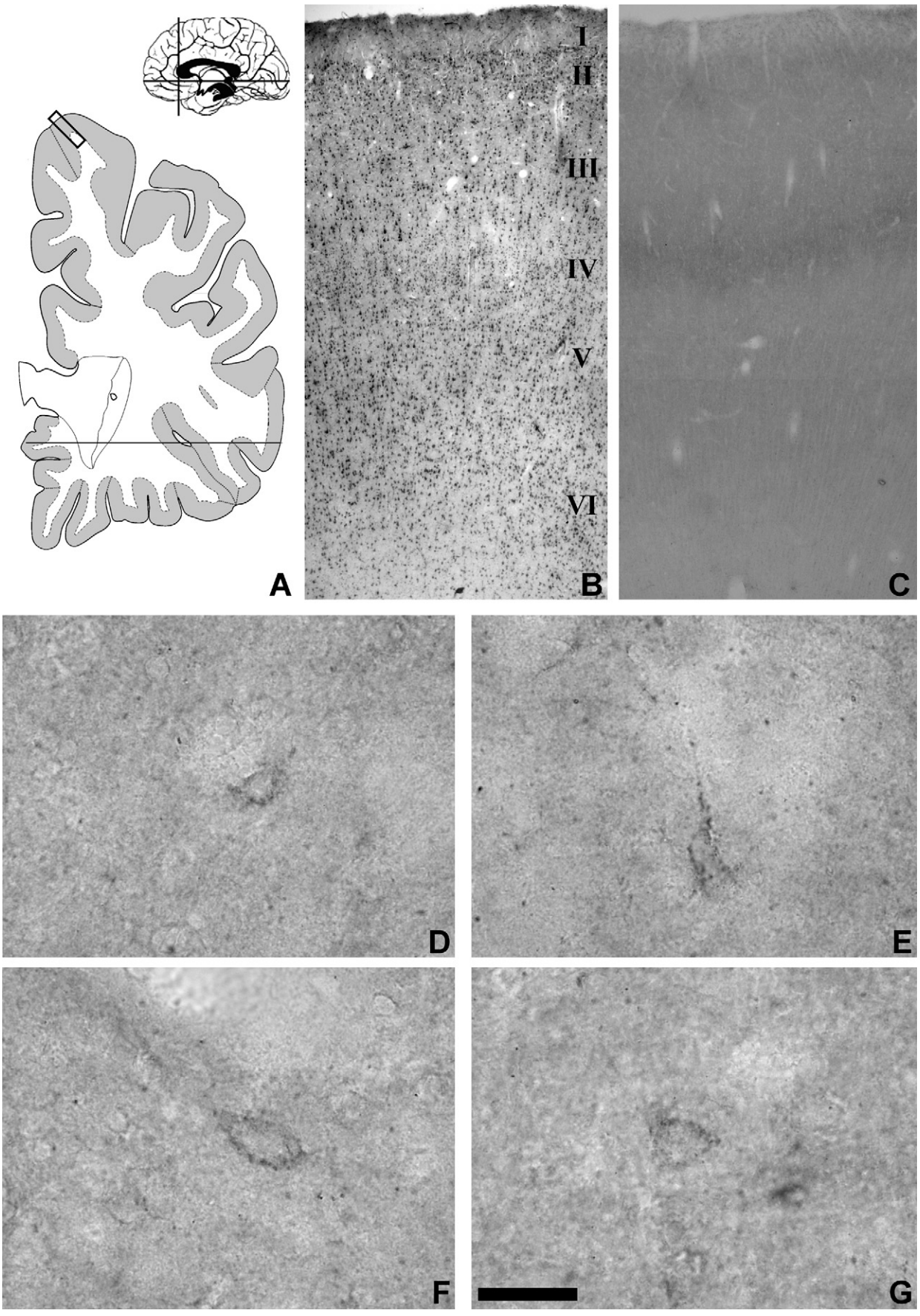
The diameter of PSA-NCAM immunoreactive cells was estimated studying 98 cells from all the samples used in our study. The maximum diameter of each of these cells was measured and the total result was expressed as the mean diameter in microns ± S.E.M. In order to estimate the density of PSA-NCAM expressing neurons, labeled cells were plotted in cortical traverses using an Olympus microscope equipped with a camera lucida at 100× magnification. Neuronal profiles were expressed as mean values (±standard errors) per mm^2, and were the result of counts on one slide of five random cortical traverses, from the pial surface to the white matter border, in each subject.

All sections processed for fluorescent immunohistochemistry were mounted on slides and coverslipped using Permafluor mounting medium (Immunon/Shandon, Pittsburgh, PA). Then, the sections were observed under a confocal microscope (Leica TCS-SP2). Z-series of optical sections (1 μm apart) were obtained using sequential scanning mode. These stacks were processed with LSM 5 Image Browser software. Fifty immunoreactive cells were analyzed in each case to determine the co-expression of PSA-NCAM and the markers of mature neurons, interneurons or glial cells described before.

3. Results

3.1. PSA-NCAM distribution in the human prefrontal cortex

A laminated pattern of staining could be observed in the neuropil of the PFC sections stained with anti-PSA-NCAM antibody (Fig. 1). Layers III–IV displayed intense PSA-NCAM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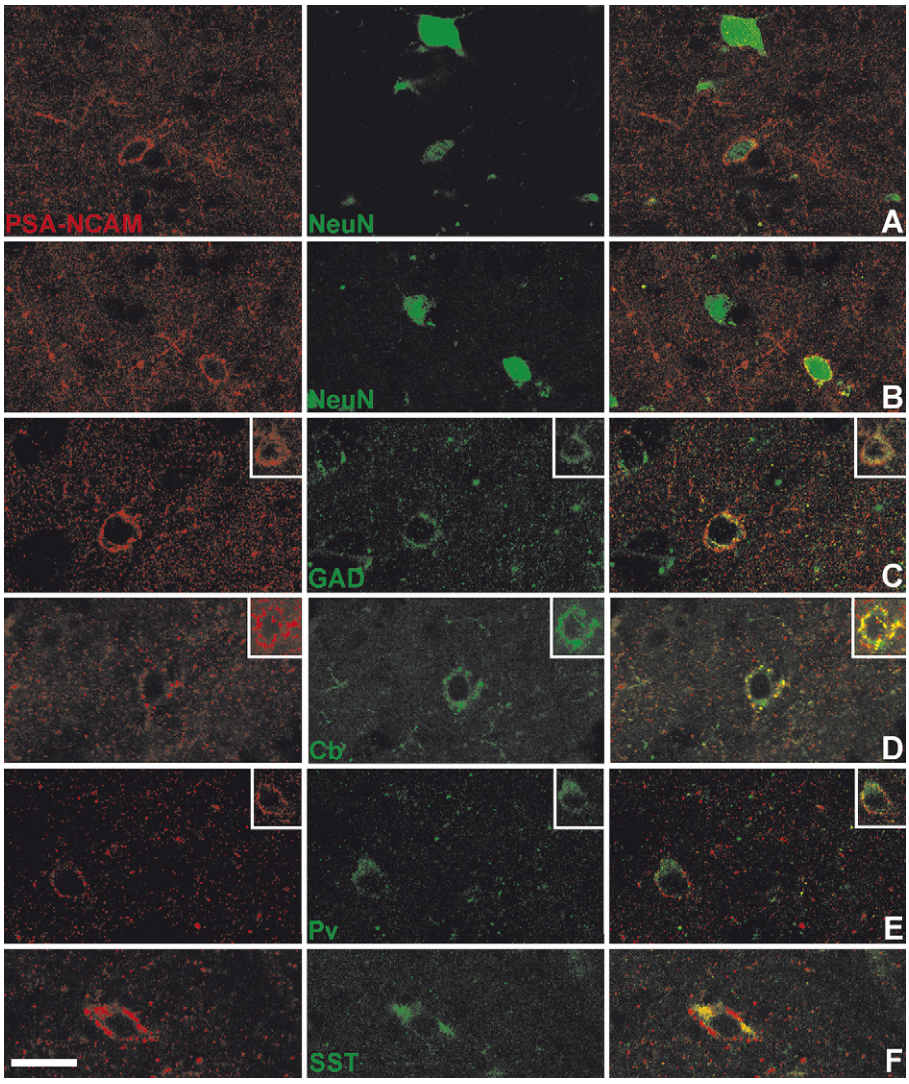

Fig. 2. Characterization of the phenotype of PSA-NCAM immunoreactive neurons in the human medial prefrontal cortex. (A & B) PSA-NCAM/NeuN immunoreactive neurons. (C) PSA-NCAM/GAD67 immunoreactive neuron. (D) PSA-NCAM/Calbindin-D28K immunoreactive neuron. (E) PSA-NCAM/parvalbumin immunoreactive neuron. (F) PSA-NCAM/somatostatin immunoreactive neuron. All photographs in this figure correspond to single optical sections taken from z-stacks. The inserts in figures C and D are 2D projections of 4 consecutive (1 μm) optical sections. Scale bar: 20 μm.

expression, while layer Vb displayed lower intensity. The other layers showed faint PSA-NCAM expression in their neuropil, which was absent in the white matter. This pattern has been observed in all the human samples analyzed. The mean density of PSA-NCAM expressing cells in the sections of PFC studied was 6.1 ± 2.2 cells/mm^2. PSA-NCAM expressing cells were found in all the studied layers, although they were less abundant than in the rodent PFC. They were usually small cells (mean diameter 11.0 ± 0.53 μm), which displayed immunoreactivity around the cell somata and the proximal processes (Fig. 1D–G). PSA-NCAM immunoreactive cells did not display pyramidal morphology and their somata were smaller than those of these excitatory neurons. Some PSA-NCAM expressing cells could be also observed in the white matter beneath the PFC.

3.2. Phenotype of PSA-NCAM expressing cells

The phenotypic characterization of PSA-NCAM expressing cells, using double immunohistochemistry, revealed that virtually all of them were mature neurons (98% were NeuN immunoreactive), including those located inside the white matter (Fig. 2A and B). PSA-NCAM expressing cells in the PFC did not co-express markers of astrocytes (GFAP) or

Fig. 1. (A) Schematic drawing of a section of the human brain indicating the portion of the rostromedial superior frontal gyrus analyzed in our study. Adapted from "The atlas of the human Brain" Mai et al., 2004. (B) Panoramic view of the human medial prefrontal cortex (mPFC) stained with toluidine blue. (C) Panoramic view of and adjacent section to that in A, showing the distribution of PSA-NCAM immunoreactivity. Observe the presence of a band of medium intensity immunoreactivity located in the deep part of layer III and another band with lower intensity located in layer V. (D–G) PSA-NCAM immunoreactive neurons located in the human mPFC. D: in layer VI. E: in layer II, F & G: in layers III and V respectively. Scale bar: 500 μm for B and C; 20 μm for D–G.

oligodendrocytes (rip). None of the prefrontocortical PSA-NCAM immunoreactive cells expressed doublecortin (DCX), a microtubule associated protein which is considered a reliable marker of recently generated neurons, at least in the hippocampus (Brown et al., 2003). In fact, we did not observe any DCX expressing cell in the human PFC. This protein is also expressed by certain neurons in the temporal lobe of adult rats, which have not been recently generated (Nacher et al., 2001). In order to validate our DCX immunostaining, we have examined some sections of human entorhinal cortex and we have also found DCX expressing cells located in layer II.

Many of the PSA-NCAM immunoreactive neurons in the human PFC also displayed GAD67 immunoreactivity (50%), indicating that, at least part of them, were inhibitory neurons (Fig. 2C). These results were in accordance with previous data from our laboratory in the mPFC of rats (Varea et al., 2005). There were no differences, attending to their morphology, between PSA-NCAM expressing neurons co-expressing GAD67 and those which did not co-express it. Co-localization was more frequent in deeper cortical layers and the white matter than in superficial layers: Usually, PSA-NCAM expressing neurons located in layers I–III did not display GAD67 immunoreactivity. Moreover, when observed with NeuN immunostaining, neurons displaying pyramidal morphology were always devoid of PSA-NCAM immunoreactivity. In order to further characterize PSA-NCAM immunoreactive interneurons, we performed double immunohistochemistry against PSA-NCAM and different markers for interneurons, which have already been found in PSA-NCAM expressing neurons of the rat medial prefrontal cortex (mPFC). Forty-eight percent of PSA-NCAM immunoreactive neurons expressed calbindin (Fig. 2D), 6% expressed parvalbumin (Fig. 2E), 22% expressed somatostatin (Fig. 2F), but none of the PSA-NCAM expressing neurons analyzed showed calretinin immunoreactivity. In agreement with our previous observations in the rat mPFC, we did not find any PSA-NCAM immunoreactive neuron expressing CCK or VIP in the human PFC. However, contrarily to what happens in the rat, PSA-NCAM expressing cells do not show NPY immunoreactivity, although, in some cases, NPY immunoreactive fibers were found in their close vicinity.

4. Discussion

This study reports the characterization of PSA-NCAM expression in the rostromedial region of the frontal superior gyrus of the human dorsolateral PFC (Brodmann area 9). We have selected this cortical region in order to compare its PSA-NCAM expression pattern with that in the rat medial PFC (Varea et al., 2005). Although the rat cortical fields are less differentiated and less segregated than those in the primate cerebral cortex, rats have a prefrontal cortex, part of which (the anterior cingulate and the prelimbic cortices) displays anatomical and functional features that resemble characteristics of the primate dorsolateral prefrontal cortex (Uylings et al., 2003). We have observed a laminated pattern of expression of PSA-NCAM and the presence of PSA-NCAM expressing cells in all layers (including the white matter). The phenotypic characterization of these cells reflects that they are mature neurons, many of which can be characterized as interneurons. We compare the phenotype of PSA-NCAM expressing neurons in the human PFC with our previous description in the rat (Varea et al., 2005). The role of PSA-NCAM in the structural plasticity of the PFC is also discussed. Finally, our results are interpreted in light of the ''neuroplastic'' hypothesis on the etiology of certain psychiatric disorders.

4.1. Phenotype and distribution of PSA-NCAM expressing cells in the human medial prefrontal cortex

Our analysis reveals that most, if not all, PSA-NCAM expressing cells in the human PFC are mature neurons, as indicated by their NeuN expression (Mullen et al., 1992). However, the possibility that some of these cells were recently generated should not be disregarded, because PSA-NCAM is expressed transiently by recently generated neurons born during adulthood (Rousselot et al., 1995; Seki and Arai, 1993) and recently generated interneurons have been described in the adult rat neocortex (Dayer et al., 2005). This possibility is, however, unlikely, because previous studies have shown a complete lack of neurogenesis in the mPFC of adult rats (Kodama et al., 2004; Madsen et al., 2005; Wang et al., 2004) and previous results from our laboratory (Varea et al., 2005) have demonstrated that PSA-NCAM expressing neurons in the adult rat mPFC are not newly generated. Although, for obvious reasons, no pulse-chase experiments with 5'BrdU can be performed in human subjects to identify recently generated cells, our present data on double labeling with anti-PSA-NCAM and anti-doublecortin (DCX) antibodies also suggest that PSA-NCAM expressing neurons in the human mPFC are not recently generated. The microtubule associated protein DCX is widely considered a marker of recently generated neurons, although it is still present in certain regions in which no adult neurogenesis has been clearly identified (Nacher et al., 2001). We have failed to find any DCX expressing cell in the human mPFC and, consequently, none of the PSA-NCAM expressing cells in this region showed DCX immunoreactivity. However, similar to what has been described in rats (Nacher et al., 2002a), some PSA-NCAM expressing cells located in the human entorhinal cortex layer II display DCX immunoreactivity. It has to be noted, however, that GABAergic neurons born during adulthood have been described in deep layers of the rat rostral neocortex and these neurons do not co-express DCX (Dayer et al., 2005).

Most PSA-NCAM expressing neurons in the human PFC appear to be interneurons. The small size of their somata is characteristic of inhibitory neurons in the cerebral cortex. Moreover, half of them co-expressed GAD67, an enzyme exclusively expressed by inhibitory neurons. Despite this relatively low percentage of PSA-NCAM/GAD67 labeled neurons we believe that most, if not all, PSA-NCAM expressing cells in the mPFC are indeed interneurons. In fact, the lack of GAD67 expression is not sufficient to discard the inhibitory nature of a certain neuron: there are certain interneuronal populations which are devoid of GAD67 expression in their

somata but present detectable levels of this enzyme in their synaptic terminals. These interneurons have long axonal projections and they have been described in regions such as the hippocampus or the spinal cord (Barber et al., 1982; Toth and Freund, 1992). Some of the PSA-NCAM expressing neurons also express somatostatin, parvalbumin or calbindin. In the cerebral cortex, the two former proteins appear to be exclusively expressed by GABAergic interneurons, while the later is also found, although faintly expressed, in pyramidal neurons (del Rio and DeFelipe, 1996; Miettinen et al., 1996; Morino-Wannier et al., 1992). However, the hypothesis on the interneuronal nature of PSA-NCAM expressing cells is also supported by two of our present observations: (1) none of the PSA-NCAM immunoreactive neurons displayed pyramidal morphology and (2) pyramidal neurons observed with NeuN immunostaining never showed PSA-NCAM expression. Similar results have been found in the rat mPFC (Varea et al., 2005). A recent report has described PSA-NCAM expression in chandelier terminals in layers II and III of the human entorhinal cortex and temporal neocortex, which correspond to parvalbumin expressing interneurons (Arellano et al., 2002). We only have observed a very low proportion of PSA-NCAM immunoreactive neurons co-expressing parvalbumin in the human mPFC and, in contrast with the study of Arellano et al. (2002) we have not observed clear PSA-NCAM immunoreactivity in any of the proximal axonal segments of pyramidal neurons of the PFC. These results are in agreement with what we observed in the rat, where PSA-NCAM immunoreactive structures never co-expressed parvalbumin (Varea et al., 2005). This suggests that regional differences exist in the phenotype of cortical PSA-NCAM expressing interneurons.

4.2. PSA-NCAM expression in the neuropil of human medial prefrontal cortex

PSA-NCAM expression in the PFC neuropil may originate from local PSA-NCAM expressing neurons or it may come from neurons in other cerebral regions, which project to the PFC. Although the phenotype of PSA-NCAM expressing puncta in the neuropil cannot be clearly established in our human samples due to the histological quality of the tissue, based on our recent study in rats (Varea et al., 2005), we consider that the first possibility is more likely. We have found that many PSA-NCAM expressing puncta in the rat mPFC neuropil co-express GAD67 and thus should correspond to intrinsic elements, probably belonging to PSA-NCAM expressing interneurons (Varea, Gomez-Climent and Nacher unpublished observations). However, we cannot reject the possibility that some of the PSA-NCAM expressing elements in the neuropil may come from other cerebral areas projecting to this cortical region. Although little is known about the afferent connections to the human PFC, in other mammals, the hippocampus, the amygdala, some thalamic nuclei and other cortical regions project to the PFC (Bacon et al., 1996; Conde et al., 1995; Datiche and Cattarelli, 1996; Delatour and Witter, 2002; Krettek and Price, 1977). Some of these areas display high levels of PSA-NCAM expression during adulthood (Bonfanti et al., 1992; Nacher et al., 2002b; Seki and Arai, 1991a) and may be responsible for the presence of this molecule in the PFC neuropil. However, electron microscopy studies must be performed in order to characterize the subcellular location of this molecule and to infer whether it is located in synapses. If this were the case, the nature of these synapses and the postsynaptic or presynaptic location of PSA-NCAM expression should be also determined.

4.3. PSA-NCAM and structural plasticity in the human prefrontal cortex

PSA-NCAM is implicated in structural plastic events such as cell migration, neurite extension/retraction (Rutishauser and Landmesser, 1996; Zhang et al., 1992) or synaptic reorganization (Miragall et al., 1988; Seki and Rutishauser, 1998). This molecule is widely expressed during CNS development and it is strongly downregulated during adulthood in rodents. However, some regions of the adult CNS retain high levels of PSA-NCAM expression, such as the hypothalamo-neurohypophyseal system (Theodosis et al., 1994), the olfactory bulb (Miragall et al., 1988) the piriform and entorhinal cortices (Seki and Arai, 1991a), the amygdala (Nacher et al., 2002b), the hippocampus (Seki and Arai, 1991b) and the mPFC (Varea et al., 2005). Interestingly, in all of these regions structural plastic processes, such as neurite or spine remodeling and synaptic reorganization, have been described in adult animals. To date, the hippocampus and the entorhinal and temporal cortices (Arellano et al., 2002; Barbeau et al., 1995; Mikkonen et al., 1999) are the only regions of the adult human brain in which the presence of PSA-NCAM has been characterized. Our present results extend these previous observations to the PFC and suggest that this molecule may also mediate structural plastic events in this human cortical region. Although there is not yet a comprehensive study on PSA-NCAM expression in the human amygdala, preliminary results from our laboratory indicate that PSA-NCAM expressing cells can also be found in this limbic area in humans, which suggests that the distribution of this molecule is similar in humans and rodents.

Although our results in the PFC of rats (Varea et al., 2005) and humans (present results) appear to indicate that PSA-NCAM is exclusively expressed by interneurons, it is interesting to note that the structural plasticity occurring in this cortical region has only been described in pyramidal neurons (Brown et al., 2005; Cook and Wellman, 2004; Radley et al., 2004, 2005; Vega et al., 2004). The role of PSA-NCAM in the remodeling of prefrontocortical neurons still remains unknown. However, it is likely that changes in PSA-NCAM expression may control the degree of inhibitory neurotransmission onto principal neurons by promoting or blocking the detachment of inhibitory synapses. Whether these structural modifications occur in vivo and whether they are related to the pyramidal neuronal remodeling observed after chronic stress and other conditions, still remains to be determined. Interestingly, a recent study has shown that over a prolonged period of time, the only neurons exhibiting dynamic arbor rearrangements in the neocortex of control adult rodents are interneurons,

while pyramidal cells remained stable (Lee et al., 2005). The expression of PSA-NCAM in certain interneurons may separate them physically from synaptic inputs and outputs. This may indicate that these cells constitute a subpopulation of ''dormant'' interneurons. If true, this fact may have very important implications in the control of inhibitory neurotransmission in the cerebral cortex. In support of this idea, we have recently observed that PSA-NCAM expressing cells in adult CNS rarely express proteins related to cellular activation, such as ARC, c-Fos or c-Fos-related antigens (Nacher et al., unpublished results). Whether PSA-NCAM expression in prefrontocortical interneurons and, consequently, this putative disconnection are transient or permanent, still remains to be determined. Given this involvement of PSA-NCAM in neuronal structural plasticity, it would be interesting to analyze the expression of this molecule in the PFC of depressed and schizophrenic patients, because recent hypotheses suggest that alterations in the structural plasticity of neuronal networks may also be involved in these mental disorders (Castren, 2005; Duman et al., 2000; Frost et al., 2004).

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