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ASTROCYTE EXPRESSION OF D2-LIKE DOPAMINE RECEPTORS IN THE PREFRONTAL CORTEX

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Abstract

The dopaminergic system is of crucial importance for understanding human behavior and the pathogenesis of many psychiatric and neurological conditions. The majority of studies addressing the localization of dopamine receptors (DR) examined the expression of DR in neurons, while its expression, precise anatomical localization and possible function in glial cells have been largely neglected. Here we examined the expression of D2-like family of DR in neuronal and glial cells in the normal human brain using immunocytochemistry and immunofluorescence. Tissue samples from the right orbitomedial (Brodmann's areas 11/12), dorsolateral (areas 9/46) and dorsal medial (area 9) prefrontal cortex were taken during autopsy from six subjects with no history of neurological or psychiatric disorders, formalin-fixed, and embedded in paraffin. The sections were stained using novel anti-DRD2, anti-DRD3, and anti-DRD4 monoclonal antibodies. Adjacent sections were labeled with an anti-GFAP (astroglial marker) and an anti-CD68 antibody (macrophage/microglial marker). The pyramidal and non-pyramidal cells of all three regions analyzed had strong expression of DRD2 and DRD4, whereas DRD3 were very weakly expressed. DRD2 were more strongly expressed in layer III compared to layer V pyramidal neurons. In contrast, DRD4 receptors had a stronger expression in layer V neurons. The most conspicuous finding was the strong expression of DRD2, but not DRD3 or DRD4, receptors in the white matter fibrous astrocytes and in layer I protoplasmic astrocytes. Weak DRD2-immunoreactivity was also observed in protoplasmic astrocytes in layers III and V. These results suggest that DR-expressing astrocytes directly participate in dopaminergic transmission of the human prefrontal cortex.

Keywords

Astrocytes • Depression • Dopamine receptors • Drug abuse • Monoclonal antibodies • Prefrontal cortex • Schizophrenia

1. Introduction

The dopaminergic system subserves many aspects of normal human behavior and is involved in the pathogenesis of a number of psychiatric and neurological conditions, such as schizophrenia, drug abuse, and depression [1]. There is evidence that projections from midbrain dopaminergic neurons to limbic regions of the ventral striatum, amygdala, hippocampus and the prefrontal cortex (PFC) comprise the core of the universal brain reward system [2]. The firing frequency of these dopaminergic ventral tegmental area (VTA) neurons (mainly from the A10 group) increases during any naturally occurring pleasant experience of eating food, during sexual activity or while bonding with a child ("behavioral activation"), whereas long-term changes and alterations in synaptic plasticity of these projections that may result from lack of care during early postnatal period can lead to profound and lasting changes in emotional development, attachment behavior, and their increased responsiveness to stress and stimulants (for a review see [3]).

Tyrosine hydroxylase is the rate limiting enzyme for dopamine synthesis, as well as for the synthesis of noradrenaline and adrenaline. However, several studies in primate species have showed that tyrosine hydroxylase and dopamine beta-hydroxylase (that is required for noradrenaline synthesis) are not colocalized in immunoreactive neurons. Tyrosine hydroxylase is therefore considered as a reliable marker for dopaminergic projections and neurons in primates [4]. Comparative analysis of tyrosin-hydroxylase-immunoreactive axon length density has revealed that humans and chimpanzees together deviated from macaques in having increased dopaminergic afferents in layers III and V/VI of Brodmann's areas 9 and 32 of PFC [5]. Such phylogenetic differences suggest a potential role for dopamine in the expansion of the neocortex and evolution of cognitive capabilities [4,6,7].

There are five subtypes of dopamine receptors, divided into two families: D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors. These five dopamine receptors are all members of the superfamily of seven transmembrane domain, G-protein coupled receptors. The assignment of a cloned receptor to one of these families was based on shared pharmacological features, second messenger coupling, and conserved structural features among individual receptors. The D1-like dopamine receptors

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consist of the D1 and the D5 receptors, which are coupled to adenylate cyclase through G_s. The D2-like family of receptors are coupled through inhibitory G-proteins (thus mediating inhibitory neurotransmission) and have high affinities for a number of drugs with antipsychotic properties, although each receptor subtype has unique pharmacological features. For example, the D2 and D3 receptors have high affinity for raclopride, while the D4 receptor has a particularly high affinity for clozapine [8]. Interest in clozapine stems from its effectiveness in reducing positive and negative symptoms in acutely psychotic and treatment-resistant schizophrenic patients without eliciting extrapyramidal side effects [9].

So far, the majority of studies addressing the localization of dopamine receptors (DR) in the human brain used dopamine receptor mRNA expression [10-12] or ligand binding [13-17]. These studies showed that the strongly expressed mRNA for dopamine receptors in PFC is DRD1 and DRD4 mRNA, other DR receptors being expressed in lower amount. Among the less abundantly expressed receptors, DRD2 has the strongest expression, and the DRD3 has the lowest expression.

In the primate PFC, the D2 dopamine receptors are localized in both pyramidal cells [18] and interneurons [19-21]. The strongest expression of DRD2 mRNA was found in the pyramidal cells of the layers II-III and V-VI [22,23]. The D4-receptor antibody labelled GABAergic neurons in many regions of the cerebral cortex, but also in a subset of cortical pyramidal cells [9]. However, the anatomical localization of DRD2 receptors and their possible function in astrocytes of PFC has not yet been examined. The first report directly relating the effect of dopamine on astrocytes was by Henn and colleagues [24], who documented the presence of large amount of haloperidol-binding sites on astrocyte membranes. More recently, using immunohistochemical methods [20,21,25,26] and RT-PCR [25], D2-like receptors were found mainly in the interneurons, pyramidal neurons, and in astroglial processes. Measuring specific binding activity in isolated astrocytes from the cerebral cortex of human, monkey, rat, and mouse preparations, Khan and collaborators determined that approximately 35% of the total binding activity of the compounds with high affinities for D2-like receptors was associated with astrocytes [20].

Considering the evidence that astrocytes may play an active role in neural communication [27], in the present report we have focused on the expression of D2-like family of DR in two main astrocyte subclasses in normal human PFC using a panel of novel monoclonal antibodies [28].

2. Materials and methods

2.1 Tissue preparation

Tissue samples from the right orbitomedial (areas 11/12), dorsolateral (areas 9/46) and dorsal medial (area 9) PFC were taken during autopsy from six subjects (age range: 48-63 years) with no history of neurological or psychiatric disorder. The causes of death were myocardial infarction in five cases, and suicide in one case. The postmortem intervals ranged from 6 to 24 hours. Following fixation in 4% formaldehyde in phosphate buffer saline (PBS, pH = 7.4) for exactly two weeks, each block of tissue was cut in the rostrocaudal direction in several slabs. Slabs were dehydrated through a graded series of ethanol solutions, cleared in toluene, embedded in paraffin (Histowax, Jung, Nussloch, Germany) and serially cut in 12 µm-thick sections. After deparaffinization in xylene, the sections were rehydrated and used either for immunohistochemistry or Nissl stain. For Nissl staining the sections were collected in 70% ethanol, placed in 50% and then in 5% ethanol, then rinsed in distilled water, and finally in a staining solution consisting of one part of 0.5% cresyl violet in distilled water mixed with four parts of distilled water. Upon achieving adequate staining, the sections were placed in distilled water, then dehydrated through a graded series of alcohol solutions and finally in ether–ethanol solution (two parts of ether and one part of 100% ethanol), rinsed with xylene, and mounted.

2.2 Immunohistochemistry

To eliminate endogenous peroxidases and nonspecific staining, tissue sections were pretreated for 20 min in 0.3% hydrogen peroxide. The sections were incubated with a blocking solution consisting of PBS containing 5% BSA and 0.5% Triton X-100 (Sigma, St. Louis, MO, USA) for 1 hour at room temperature. The primary antibodies against the N-terminus of DRD2 (MANDOP 21, clone 1D7), DRD3 (MANDOP31), and DRD4 (MANDOP 41) were diluted in 2% PBS/0.25% normal donkey serum in Triton X-100 and incubated on the slide overnight at 4°C. Subsequently, the sections were incubated with secondary biotinylated anti-mouse antibody in blocking solution (1:200) for 1 hour at room temperature (Vectastain ABC kit, Vector Laboratories, Burlingame, USA). Following another washing, Vectastain ABC reagent streptavidin-peroxidase complex) was applied for 1 hour at room temperature and washed. Finally, peroxidase activity was visualized using Ni-3,3′-diaminobenzidine (DAB) (Sigma). The specificity of the DRD2, DRD3, and DRD4 antibodies used has been previously characterized by Western blot analysis and immunocytochemistry [28]. The specificity was further confirmed in sections by obtaining no specific staining (negative controls) upon the use of preimmune serum or upon omission of the primary antibodies.

Immunohistochemistry for glial fibrillary acidic protein (GFAP) was performed using an anti-cow GFAP monoclonal rabbit IgG (Dako, Copenhagen, Denmark) in dilution 1:500, whereas expression of macrophage/microglial marker CD68 was revealed using a primary rat anti-mouse CD68 antibody (Serotec Ltd, Kidlington, Oxford, UK, cat. No. MCA1957) at 1:80 dilution.

3. Results

The pyramidal and non-pyramidal cells of all three PFC regions analyzed had strong expression of DRD2 and DRD4 receptors, whereas DRD3 receptors were very weakly expressed. DRD2 receptors were more strongly expressed in layer III compared to layer V pyramidal neurons. In contrast, DRD4 receptors had a stronger expression in layer V pyramidal neurons (Figure 1).

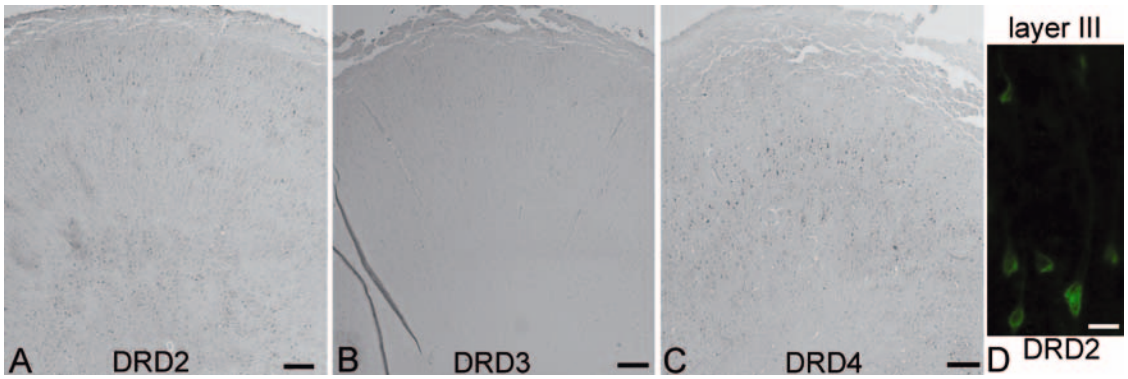

Figure 1. Comparison of laminar expression of DRD2, DRD3, and DRD4 in the orbitomedial prefrontal cortex. Pyramidal cells of layers III and V and interneurons have the strongest DRD2 (A, D) and DRD4 immunoreactivity (C), whereas DRD3 expression is very weak (B). Note the numerous DRD2-immunoreactive astrocytes in the white matter and layer I. Occasionally, DRD2-expressing astrocytes were also found in cortical layers. Scale bars = 200 µm (A-C), and 20 µm (D).

The most conspicuous finding was the strong expression of DRD2, but not DRD3 or DRD4, receptors in the cell bodies and processes of white matter fibrous astrocytes and layer I protoplasmic astrocytes (Figure 2). In most sections the complete morphology of these cells could be clearly seen. Fine and long processes that expanded radially and symmetrically from the cell body, together with the specific subcortical and cortical localization of the cells, indicated that these cells were fibrillary and protoplasmic astrocytes. To confirm this conclusion, adjacent sections were stained with the astrocytic marker GFAP and a marker for activated microglia, CD68. The localization and morphology of DRD2- and GFAP-immunoreactive astrocytes were similar. The DRD2-expressing astrocytes were particularly numerous in layer I and subcortical white matter (Figure 2). Towards the deep white matter, the number of DRD2-immunoreactive astrocytes diminished. Occasionally, these cells could also be found in the cortex – either in layer V (Figure 3), or layer III. We found no evidence of astrogliosis in any of the brain samples analyzed. Furthermore, staining with CD68 showed no evidence of microglial activation.

4. Discussion

4.1 PFC dopaminergic afferents

Although there are many similarities in the distribution of the dopaminergic afferents in rat and primate brain, comparative analysis of regional and laminar distribution of dopaminergic afferents to the cerebral cortex has shown clear differences between rodents and primates [29-32]. In comparison to rodents, the dopaminergic input to the cerebral cortex in non-human primates and humans is vastly expanded in terms of cortical regions that receive these projections [29-31]. The mesencephalic dopamine-projecting neurons populations are only 10-20 times larger in primates than in rodents [33], with in humans a cortical surface about 400 times larger, suggesting a high level of axonal collateral ramification for each dopaminergic neuron.

Furthermore, unlike in rodents, layer I in primates is the most densely innervated layer throughout the whole cortical mantle, including the PFC [34]. Together with dense network of dopaminergic terminals in layers V and VI, dopaminergic afferent projections form characteristic bilaminar pattern that has major functional implications for cortical processing [35]. Based on these findings, it can be concluded that the afferent dopaminergic projections to the human cerebral cortex, particularly those to the medial PFC, orbital PFC and cingulate cortex are among the strongest and display characteristic laminar patterns. Moreover, the greater numbers of dopaminergic terminals in layer III of the primate frontal cortex also suggest an important modulatory role of dopamine on corticocortical connections [36]. Also in contrast to rodents, dopaminergic

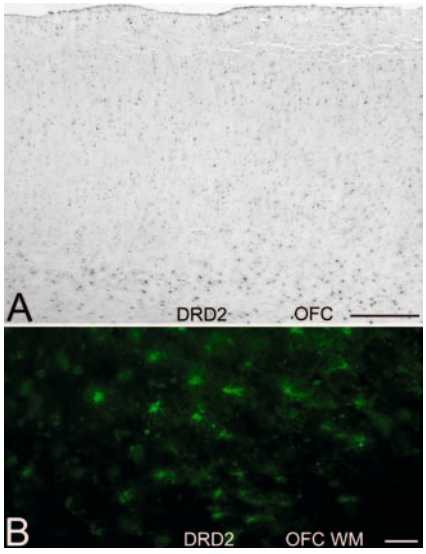

Figure 2. Distribution of DRD2-immunopositive astrocytes in the orbitomedial PFC. Strong DRD2 receptors expression of astrocytes in layer I and subcortical white matter (A). Immunofluorescence of DRD2 expression in astrocytes in subcortical white matter (B). Scale bars = 500 µm (A) and 50 µm (B). OFC WM = orbitofrontal cortex white matter.

afferents in monkey and human fetuses reach their prospective cortical targets as early as the first half of gestation, displaying the same regional and laminar distribution at birth as in adulthood, whereas in rodents some of dopamine afferents reach its cortical targets only after birth [37]. Our observation that the astrocytes in layer I and pyramidal and non-pyramidal neurons in the infragranular layers

strongly express specific DRD2 receptors therefore fits well with the known bilaminar distribution of dopaminergic fibers in the primate PFC [29-32].

4.2 PFC dopaminergic receptors

The distribution of dopamine receptor mRNAs in human neocortex is significantly different from what had been reported in the rat brain, likely reflecting reported differences between rodents and primates in the dopaminergic innervation of the cortex [5,32,38,39]. The importance of these differences is further supported by the findings that primates have an accelerated rate of protein evolution for the dopamine receptor gene *DRD2* (relative to rodents) and that mouse knockout of *DRD2* exhibit defects in acquiring reward-mediating behavior [40]. Additional lines of evidence suggest that humans appear to be uniquely susceptible to a number of neuropsychiatric disorders presenting with cognitive deficits, such as schizophrenia, and that this susceptibility may be due to an increased reliance on dopaminergic systems to support intellectual capabilities [1,5,41].

In human, all five mRNAs for dopaminergic receptors are expressed in the neocortex at much higher levels than in the rat. While the distributions of DRD1 and DRD2 receptor mRNA in the rat and human appear similar, the expression of DRD3, DRD4, and DRD5 are strikingly different. Neither DRD3 nor DRD4 receptor mRNA have been consistently demonstrated in the rat neocortex. In human, however, both DRD3 and DRD4 mRNAs are found. The D3 receptor mRNA is clearly the rarest of the dopamine receptor transcripts in human neocortex [23]. On the other hand, the DRD4 receptor mRNA is enriched in the human cortex, and may be the predominant form of D2-like mRNA expression in most regions surveyed. The DRD5 receptor mRNA has a pattern similar to that of the DRD2 receptor, which is both unusual and unexpected, given its lack of cortical distribution in the rat [23]. In PFC regions, the mRNAs encoding the DRD1 and DRD4 receptors are the most abundant of the five receptor transcripts and can be observed in both infra- and supragranular layers [23].

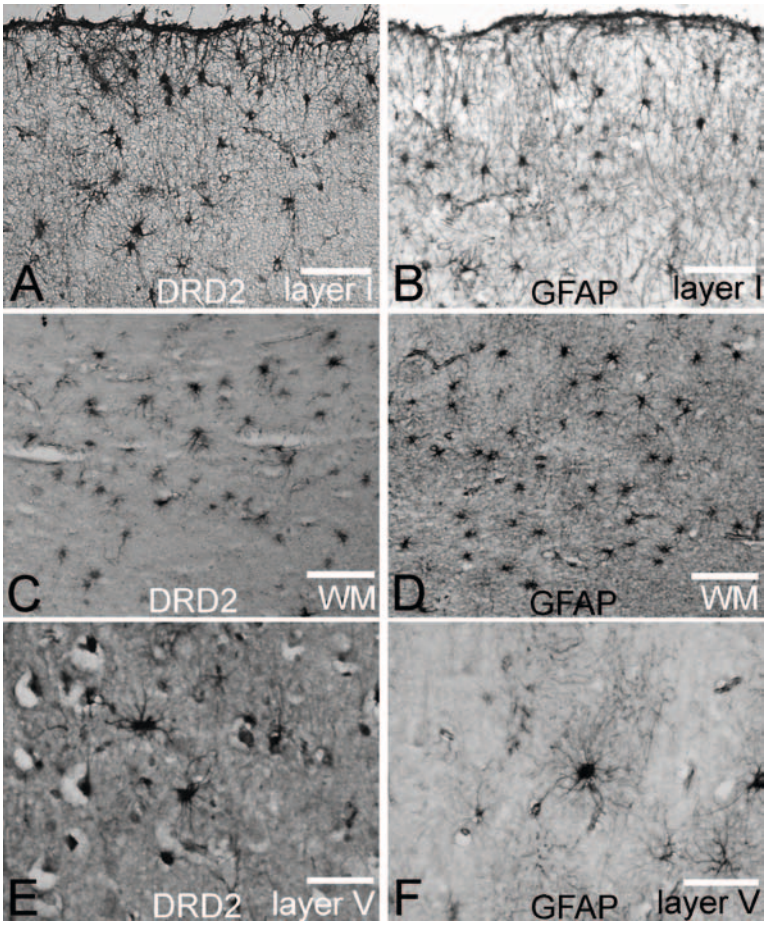

Figure 3. Layer I protoplasmic astrocytes have short, thick, and highly branched processes that express DRD2 receptors (A). C) Fibrous astrocytes of the white matter have long, thin and less branched DRD2-positive processes. E) DRD2-positive positive pyramidal cells, interneurons and astrocytes in layer V. Panels B, D and F show GFAP immunocytochemistry of the sections adjacent to A, C, and E, respectively. WM, white matter. Scale bars A-D = 100 µm, E and F = 50 µm.

Our observation that the pyramidal and non-pyramidal cells of all three PFC regions analyzed had strong expression of DRD2 and DRD4 receptors, whereas DRD3 receptors were very weakly expressed is mostly in accordance with the known distribution of mRNA for dopamine receptors [9,22,23]. As the mesocortical dopaminergic pathway to PFC has been commonly related to various psychiatric disorders, such as schizophrenia, it is possible that the action of drugs targeting the dopaminergic system, particularly antipsychotic drugs, could mediate at least a part of their effect through the modulation of astrocytic functions. Results of some *in vitro* experiments have already drawn attention to this possibility: treatment with dopamine upregulates FGF2 mRNA expression in cortical and striatal rat astrocytes [42], whereas dopamine agonists increase the secretion of NGF and GDNF in cultured mouse astrocytes [43]. Furthermore, it has been shown that atypical neuroleptic drugs upregulate DRD2 expression in astrocyte cultures [44].

In this context, our results suggest an active role of astrocytes expressing dopaminergic receptors in the human PFC. Consequently, alterations of glial DR expression may have clinical implications with respect to function of PFC and its disturbances in schizophrenia, drug abuse, depression and other psychopathological states.

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