DOPAMINE D5 RECEPTORS OF RAT AND HUMAN BRAIN

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Abstract—In contrast to dopamine D1 receptors, the anatomical distribution of D5 receptors in the CNS is poorly described. Therefore, we have studied the localization of dopamine D5 receptors in the brain of rat and human using our newly prepared subtype-specific antibody. Western blot analysis of brain tissues and membranes of cDNA transfected cells, and immunoprecipitation of brain dopamine receptors suggest that this antibody is highly selective for native dopamine D5 receptors. The D5 antibody labeled dopaminergic neurons of mesencephalon, and cortical and subcortical structures. In neostriatum, the D5 receptors were localized in the medium spiny neurons and large cholinergic interneurons. The D5 labeling in caudate nucleus was predominantly in spines of the projection neurons that were frequently making asymmetric synapses. Occasionally, the D5 receptors were also found at the symmetrical synapses. Within the cerebral cortex and hippocampus, D5 antibody labeling was prominent in the pyramidal cells and their dendrites. Dopamine D5 receptors were also prominent in the cerebellum, where dopamine innervation is known to be very modest. Differences in the localization of D5 receptors between both species were generally indistinguishable except in hippocampus. In rat, the hippocampal D5 receptor was concentrated in the cell body, whereas in human it was also associated with dendrites.

These results show that D5 receptors are localized in the substantia nigra pars compacta, hypothalamus, striatum, cerebral cortex, nucleus accumbens and olfactory tubercle. Furthermore, the presence of D5 receptors in the areas of dopamine pathways suggests that this receptor may participate actively in dopaminergic neurotransmission.

Key words: D1-like receptors, immunoblot, immunoprecipitation, immunocytochemistry, electron microscopy, immunofluorescence.

The dopamine D5 receptor is a member of the D1-like family, which consists of D1 and D5 subtypes.11 Because of the unavailability of specific agonists and antagonists, most of the pharmacological and physiological studies do not differentiate the individual role of D1 and D5 receptors. The only major difference that has widely been recognized is that the D5 receptor displays higher affinity for the dopamine neurotransmitter than the D1 subtype11,21,37,38 which implies that the D5 subtype should participate more effectively in dopaminergic functions. However, it is the D1 subtype that has most often been described to be associated with D1-like functions. This understanding was derived from the finding that D1 receptors are predominantly localized in the primary dopaminergic projection areas, such as striatum and nucleus accumbens. But growing evidence has begun to indicate that both D1 and D5 receptors contribute individually in dopaminergic neurotransmission. For example, Kimura et al.29 have shown that D5 receptor coupling to the G-protein is stronger than D1, which is consistent with the earlier observation that D5 receptors have a higher affinity for the dopamine neurotransmitter for D5 receptors. Furthermore, blockade of D5, but not D1 dopamine receptor, suppresses reproductive behavior associated with D1 agonist (non-selective for D1 and D5 receptor) stimulation.1 More recently, Dziewczapolski et al.13 have shown that contralateral rotations induced by SKF 38393 (a D1-like agonist) in 6-hydroxydopamine lesioned rats were completely prevented by administration of an antisense oligodeoxynucleotide for the D1 receptor, whereas administration of the antisense oligodeoxynucleotide for D5 receptor potentiated the effect, indicating that D1 receptors play a facilitatory role in locomotion and D5 exert an inhibitory effect. During development, both D1 and D5 receptors also play different roles. Wang et al.39 have reported that Cajal-Retzius and migrating neurons were immunoreactive for D5 receptor, while radial glia cells were labeled with D1 receptor antibody.

The localization of the dopamine D5 receptor in rat2 and primate4 brains has been reported. However, the antibody used for the rat studies was not as rigorously tested for specificity and selectivity as the one used for the primate brain. In rat brain, the study also lacks thorough and complete information of D5 receptor distribution. Moreover, there are many discrepancies among the several studies reporting the distribution of D5 receptor mRNA in the CNS.1,3,9,21,25,32,33,37,38,40 Therefore, our aim here was to study the D5 receptor localization sites and explore the differences between rat and human brain. To achieve this we have prepared subtype-specific and selective anti-peptide antibodies against D5 receptor. An extensive characterization of the antibodies was performed to demonstrate their specificity and selectivity.

EXPERIMENTAL PROCEDURES

Materials

SCH 23390, [N-methyl-3H] (81.4 Ci/mmol) was purchased from DuPont-New England Nuclear (Wilmington, DE, USA). The (+) butaclamol-HCl was from Research Biochemicals Inc. (Natick, MA, USA). The crude membranes of recombinant S9 cells expressing dopaminergic human D1, D2L, D3rat, D4 and D5 receptors were obtained from BioSignal, Inc. (Quebec, Canada). Peptides were synthesized by the Core Facility at the School of Biological Sciences, University of Missouri-Kansas City (Kansas City, MO, USA).
Preparation of antibody to D5 receptor

A sequence common to both rat and human D5 receptor peptide DEEEGPFDRMF (corresponding to residues 428–438) was obtained from the corresponding translated cDNA sequences and synthesized. Computer assisted homology study showed that the selected amino acid sequence is exclusive for the dopamine D5 receptor subtype. An additional cysteine was added at the carboxy end of the peptide for coupling to keyhole limpet hemocyanin (KLH) protein. Peptide-KLH conjugation and rabbit immunizations were done as described earlier. A solid-phase enzyme-linked immunoassay with immobilized synthetic peptides was used to monitor antibody production. Affinity-purification of the antisera was done on the corresponding antigen peptide immobilized columns as described in detail elsewhere.

Membrane preparation and solubilization

Cortices were collected from 10 adult Sprague–Dawley rat brains after decapitation and homogenized with 10% sucrose in 50 mM Tris-HCl, pH 7.4. The homogenate was centrifuged at 3000 rpm for 5 min and microsomal membranes were prepared as described earlier. The membranes were solubilized with 1% digitonin in 50 mM Tris-HCl, pH 7.4 containing 1 mM EDTA, 5 mM KCl, 1.5 mM CaCl2, 4 mM MgCl2, 120 mM NaCl and 0.1% ascorbate for 30 min at 4°C. After centrifugation at 29,000 rpm for 1 h, the supernatant was used for immunoprecipitation and binding assays.

Immunoprecipitation of dopamine D5 receptors

The solubilized receptor membranes (800 μl containing 150 fmol of [3H]SCH 23390 binding sites) were incubated overnight at 4°C with 0–60 μl of antisera to D5. The bound dopamine receptors, as receptor-antibody complexes, were separated after incubation with 80 μl of 40% (vol/vol) suspension of protein-A agarose followed by centrifugation. The non-immunoprecipitated receptors in supernatant were assayed for [3H]SCH 23390 binding. For the binding, 500 μl of supernatant was incubated with 2 nM of radioligand for 1 h at 22°C in total volume of 1.0 ml of 50 mM Tris-HCl (pH 7.4) containing 1 mM EDTA, 5 mM KCl, 1.5 mM CaCl2, 4 mM MgCl2 and 120 mM NaCl. The reaction was stopped by rapid filtration through 0.3% polyethyleneimine soaked Whatman GF/B filters and washed three times with 50 mM Tris-HCl, pH 7.4. Filters were dried and counted. The non-specific binding of the dopamine receptors was determined in the presence of 2 μM (+) butaclamol-HCl. The amount of immunoprecipitated receptors was calculated after subtracting the values of supernatant from total specific binding (100%) of [3H]SCH 23390. The 100% values are representative of 0 μl of D5 antibody or 60 μl pre-immune serum treated supernatant.

Immunoblots

Immunoblots were done according to Khan et al. Briefly, rat cortical and striatal membrane proteins (15–20 μg/lane) were separated on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS–PAGE) and transferred to nitrocellulose membranes. The transferred nitrocellulose membranes were incubated with 5 μg/ml of affinity-purified primary antibodies to D5 which were diluted in phosphate-buffered saline (PBS) containing 0.05% Tween-20 and 1% bovine serum albumin, followed by anti-rabbit IgG (Sigma) diluted 1:100 and peroxidase anti-peroxidase (PAP) complex (Sigma) diluted with 1:100. The polypeptide bands were visualized with peroxidase reaction. For the immunoblots of membranes of the S9 cell lines expressing dopamine receptors, 4 μg of total protein was electrophoresed on 10% SDS–PAGE and transferred onto nitrocellulose membranes. The transferred nitrocellulose membranes were incubated with 5 μg/ml of affinity-purified primary antibodies to D5 which were diluted in phosphate-buffered saline (PBS) containing 10% non-fat dry milk, 5% sheep serum, 5% donkey serum and 0.1% Tween-20 for 1 h at room temperature, which was followed by incubation with 5 μg/ml antibodies to D5 for overnight at 4°C. The secondary antibody, anti-rabbit IgG-HRP (Amersham, Arlington Height, IL, USA) was diluted 1:2000 and incubated for 1 h. Immunoreactive bands were developed by using ECL kit as instructed by manufacturer (Amersham, Arlington Height, IL, USA).

Immunocytochemistry

Twelve adult male Sprague–Dawley rats (Charles River, France) of about 250 g body weight were perfused transcardially with 400 ml of 4% paraformaldehyde in 0.1 M phosphate buffer pH 7.4. Brains were then dissected out and postfixed in the same fixative for 3 h and cryoprotected with 30% sucrose. The post mortem (7–15 h intervals) human brain tissues were obtained from clinical autopsy at Carlos Haya Hospital at Malaga (Malaga, Spain). These tissues were collected from five males of 35–50-years-old without neurological or psychiatric disorders. Human brain blocks of 5 mm from motor cortex (area 4), visual cortex (area 17), prefrontal cortex (area 46), cerebellum, hippocampus and striatum were immersed in 4% paraformaldehyde in phosphate buffer, pH 7.4 for 48 h at 4°C. Blocks of human and rat brains were cut with freezing microtome (30 μm) or a Vibratome (50 μm) and processed for light and electron microscopic level studies.

Free-floating sections were processed for light microscopic level studies as described earlier. All antibodies were diluted in 0.1 M PBS with 0.3% Triton X-100. Sections were incubated for two days at 4°C in primary affinity-purified antibody to D5 (15 μg/ml) which was followed by incubation in the secondary antibody sheep anti-rabbit IgG (1:100; Sigma) or biotinylated goat anti-rabbit antibody (1:200; Jackson) and then in rabbit PAP complex (1:100, Sigma) or ABC Elite kit (1:100; Vector). The reaction was developed by using either 0.05% diaminobenzidine and 0.01% hydrogen peroxide or diaminobenzidine-glucose oxidase reaction.

For double-label immunofluorescence studies, sections were incubated with D5 antibody and mouse monoclonal tyrosine hydroxylase (TH) antibody (1:1000; Chemicon) followed by incubation with goat anti-rabbit IgG-Cy3 (1:400; Jackson) and goat anti-mouse IgG-FITC (1:100, Jackson).

For electron microscopic level analysis, Vibratome sections were incubated with D5 antibody and visualized by the immunoperoxidase method using ABC Elite kit. Sections were osmicated, dehydrated, and flat embedded in Durcupan ACM (Fluka). The resin embedded sections were cut into ultrathin sections on an ultramicrotome (Reichert) and observed in JEOL electron microscope.

RESULTS

Controls

In control experiments of western blots (Fig. 1B), immunoprecipitation and brain sections (Fig. 1C), we found that the D5 immunoreactivities were abolished by either preincubation of antibody with cognate peptide or incubation with preimmune sera. Furthermore, in immunoprecipitation experiments we observed no [3H]SCH 23390 binding activity when an unrelated antibody, anti-β of the GABA_A receptor (bd 17 from Boehringer) was used, suggesting a specific immunoreaction of D5 antibody.

Specifyity and selectivity of the dopamine D5 receptor antibody

The specificity and selectivity of the antibody was tested by immunoprecipitation of the solubilized native dopamine receptors, and immunoblots of tissue membranes and S9 cell membranes transfected with cDNA of dopamine receptors, which are shown in Fig. 1A and B. The antibody showed a concentration dependent immunoprecipitation of [3H]SCH 23390 binding sites from solubilized extract of rat cerebral cortex. The saturation point was observed at 20 μl and maintained until 60 μl (Fig. 1A), indicating the sensitivity and specificity of the D5 antibody. The antibody was able to immunoprecipitate 34.3 ± 4.8% of the total binding sites.

In both cortical and striatal tissues of rat brain, antibody to
Fig. 1. Characterization of D5 antibody by immunoprecipitation (A), immunoblots (B) and immunocytochemistry (C) studies. (A) shows D5 antibody concentration-dependent precipitation of D5 receptors as $[^3H]$SCH 23390 binding sites from rat cerebral cortex, which reached to saturation at 20 μl. The antibody was able to immunoprecipitate $34.3 \pm 4.8\%$ ($\bullet$) native D5 receptor. The remaining non-immunoprecipitated (■) binding sites may represent mostly D1 receptor and some serotonin receptor. Data represented are mean ± S.E.M. of three experiments, each done in triplicate. (B) shows the reactivity of single polypeptide band of 47,000 mol. wt in both rat cerebral cortex and striatum, which was abolished by pre-absorption of the D5 antibody with cognate peptide. However, the right panel shows the specific reactivity of antibody with D5 receptor containing recombinant cells and not with cell lines expressing several other dopamine receptor subtypes. (C) shows control immunocytochemistry of sagittal brain sections from rat cerebellum (i) and hippocampus (ii), and human cortex area 17 (iii) with D5 antibody preabsorbed with cognate peptide. M, molecular layer; P, Purkinje cell layer; G, granule cell layer; I–V, indicate the cortical layers. Scale bar = 91 μm.
the D5 receptors immunoreacted with a single protein band of 47,000 mol. wt (Fig. 1B), the expected molecular size as predicted from molecular cloning. Furthermore, in cell lines expressing dopamine receptors, the D5 antibody binds selectively to the recombinant cells transfected with D5 cDNA and showed no reactivity with cells expressing other members of the dopamine receptor family (Fig. 1B). These results demonstrate that this antibody is selective for D5 receptors.

Taken together these results suggest that this antibody is subtype-specific and selective for native dopamine D5 receptors.

Expression of the D5 receptor in midbrain

The D5 antibody showed immunoreactivity in the cell bodies of substantia nigra-pars compacta and also in pars reticulata (Fig. 2A, B). Double immunofluorescence study of D5 antibody and TH, a marker for dopaminergic cells, showed most of the neurons expressing D5 receptors are TH-positive (long tailed arrows in Fig. 2C and D). Indeed, we also observed several non-dopaminergic D5 positive neurons, most probably GABAergic (short tailed arrows in Fig. 2E and F). At electron microscopy level, the D5 immunoreactivity was often observed in neuronal dendrites, which were making asymmetric synapses with axons (Fig. 3A and B). This reactivity was associated with the plasma membranes of the neurons. Occasional presynaptic D5 receptors were also seen (Fig. 3A).

Strong labeling of D5 antibody was found in the inferior colliculus (Fig. 4A). Numerous cell bodies and their initial processes could be seen in dorsal and external cortices and central nucleus. The cells of the oculomotor nucleus and deep grey layers of superior colliculus were also immunostained (not shown).

Localization of the D5 receptor in hypothalamus and thalamus

Weak immunostaining of the D5 antibody was observed in...
the neurons of hypothalamic arcuate (Fig. 4B), mammillary (Fig. 4C) and supraoptic nuclei. However, a strong labeling of D5 receptor was seen in the thalamus (Fig. 4D–F). Reticular nucleus can be observed with a moderate immunostaining (Fig. 4D). Thalamic structures showed perikaryal labeling (Fig. 4E, F), which was dominantly present in lateral dorsal, anterior ventrolateral, anterior dorsomedial and lateral posterior thalamic nuclei.

Fig. 3. Electron micrograph of pars reticulata (A) and pars compacta (B) of substantia nigra from rat brain showing labeling of D5 receptors (arrowheads) in dendrites (d), which are making asymmetric synapse (arrow) with D5 labeled (an) and unlabeled (a) axons. Scale bar = 200 nm.

Fig. 4. Dopamine D5 receptor immunostaining in the sagittal sections of rat brain inferior colliculus (A), hypothalamic arcuate (B) and mammillary nuclei (C), thalamus (D–F), reticular nucleus (Rt; D) and globus pallidus (GP; D). Most of the labeling is associated with perikarya. LD, laterodorsal thalamic nucleus; LP, lateral posterior thalamic nucleus; VL, ventrolateral thalamic nucleus; VPL, ventral posterolateral thalamic nucleus; VPM, ventral posteromedial thalamic nucleus. Scale bars = 83 μm (A), 200 μm (B, C), 400 μm (D), 100 μm (E, F).
Fig. 5. Localization of D5 receptors in sagittal sections of subcortical forebrain areas of rat and human brains. Low magnification picture of rat striatum immunostained for D5 receptors (A), which at higher magnification (B) shows that labeling is in small size neurons (arrowheads). Strongly labeled large neurons (indicated with arrows), probably cholinergic, were also observed. However, in human striatum (C) in addition to labeling of cells, strong D5 staining was also found in dendritic fibres (arrows). (D) shows the neurofibre staining in human striatum. Neuropil immunostaining of D5 receptors was seen in accumbens nucleus (NAc; E) and islands of calleja (ICj; E and F). Tu, olfactory tubercle; VP, ventral pallidum. Scale bars = 333 µm (A), 35 µm (B), 62.5 µm (C), 20 µm (D), 267 µm (E, F).
D5 receptors in subcortical forebrain areas

In striatum, both rat and human brains were used for study. In rat, the D5 receptor was localized in the striatal medium-sized spiny neurons and large cholinergic neurons (Fig. 5A and B). However, in human, the labeling was mostly associated with the extended long dendrites (Fig. 5C and D). In striatum, at electron microscopic level, we found that D5 receptors were localized in the dendrites and spines (Fig. 6A). Often asymmetric synapses were formed on D5 containing spines. Occasional symmetric synapses were also observed. In accumbens nucleus, immunolabeling was found mainly in the neuropil (Fig. 5E). D5 receptors were also seen in the globus pallidus (Fig. 4D), islands of Calleja (Fig. 5F), olfactory tubercle and septal area.

D5 receptors in the hippocampus

In hippocampal formation, both rat and human brains were used for immunostaining studies. In rat, strong labeling of the D5 receptor was found in the pyramidal cells of hippocampus proper (Fig. 7D and F). However, in human, pyramidal cell bodies showed low labeling. Instead, their apical dendrites were more strongly stained (Fig. 7A). Human brains showed low staining in the CA1 region. In dentate gyrus of rat, D5 immunoreactivity was observed in the granule cell bodies (Fig. 7E), whereas in human, it was in the fibres of the molecular layer (Fig. 7C), presumably originating from the granule cells. The neuronal cell bodies of the dentate gyrus showed strong labeling and some of these cells were located at the border of granule cell layer and hilus (Fig. 7E). Subicular region of both the species was immunolabeled but showed similar differences as in other parts of hippocampus. In rat, D5 receptor was concentrated in neuronal cell bodies but in human it was also in their dendrites (Fig. 7B).

Localization of D5 receptor in the cerebral cortex, cerebellum and olfactory bulb

The study in cerebral cortex includes rat and several areas of human brains. D5 receptor was highly expressed in the pyramidal neurons and their dendrites (Fig. 8A–D), although we have also observed occasional non-pyramidal cells. In rat, a prominent immunoreactive neuronal band was located in layers IV–VI of frontal and limbic cortical areas (Fig. 8C and D). This band was less dense in occipital cortex. The cell body and apical dendrite of numerous pyramidal neurons were strongly labeled (Fig. 8D). In human, the labeling pattern was similar to the rat. Areas 17 and 4 showed the strongest immunoreactivity, whereas it was moderate to low in areas 1, 2 and 46. An immunoreactive cell band was also observed in all of the above areas in layers IV–VI (Fig. 8A and B). The electron microscopic analysis of area 17 from human brain indicates that D5 receptors are present in the spines, a site where asymmetric synapses are formed with afferent axons (Fig. 6B, C).

In human cerebellum, the dendritic tree of Purkinje cells showed a moderate immunoreactivity for the D5 receptor (Fig. 8E). However, occasional strongly labeled dendrites were also observed (arrows in Fig. 8E). The granule cell layer was not labeled. However in rat, apart from the Purkinje cells and their dendrites, a low reactivity was also seen in the granule cell layer (Fig. 8F).

The D5 immunoreactivity was mostly associated with the external plexiform and mitral cell layers of olfactory bulb.
DISCUSSION

The localization of D5 receptor in the dopaminergic projection neurons of substantia nigra-pars compacta was a surprise to us because earlier immunohistochemical studies in rat and monkey were unable to detect this. However, the presence of D5 mRNA transcript has been reported in different subareas of substantia nigra. The localization of D5 receptors in dopaminergic neurons suggests that this receptor may participate in the events of the nigrostriatal pathway. In rat, behavioral and neurochemical recovery from partial 6-hydroxydopamine lesions of substantia nigra was blocked by treatment with SCH 23390 (an antagonist of both D1 and D5 receptors). This observation indicates a role for the D1/D5 dopamine receptor in the development of compensatory changes in the dopaminergic neurons. D1 receptors are predominantly expressed in the neuropil of pars reticulata, whereas D5 receptors are localized in dopaminergic neurons of pars compacta. Therefore, the blocking effect produced by treatment with D1/D5 antagonists may primarily be due to the contribution of D5 receptor function. D5 receptors were also found in the substantia nigra-pars reticulata, an area which receives major input from the striatum via direct and 

(Fig. 8G) and granule cell layer of accessory olfactory nucleus (Fig. 8H).
Fig. 8. Dopamine D5 receptors in the sagittal sections of cerebral cortex, cerebellum, olfactory bulb and accessory olfactory nucleus. Pyramidal neurons with extended dendrites were found in area 17 of human cerebral cortex (A and B) as well as in frontal cortex of rat brains (C and D). Large cells of layers IV–VI were intensely labeled. In human, layers II to III staining was mostly seen in dendritic fibres as shown by arrows (A). However, in rat it was in both neurons and fibres (C). In human (E) as well as rat (F), the majority of cerebellar D5 receptors were associated with dendrites of Purkinje cells and to a lesser extent to the Purkinje cell bodies. Granular cell layer of the rat cerebellum was labeled, but in human it was not. The staining of D5 receptors was observed in the external plexiform layer (EPL), mitral cell layer (Mi) of olfactory bulb (G) and granular layer (GrA) of accessory olfactory nucleus (H). I–V, indicate the cortical layers; M, molecular layer; P, Purkinje cell layer; G, granular layer; GL, glomerular layer, IPL, internal plexiform layer; IGr, internal granular layer. Scale bars = 200 μm (A), 100 μm (B), 50 μm (C), 33 μm (D), 154 μm (E), 63 μm (F), 182 μm (G), 91 μm (H).
indirect pathways. The electron microscopic studies of the substantia nigra–pars compacta showed that the D5 receptors, which are frequently associated with dendrites, make asymmetric synapses with axons. The presynaptic localization of the D5 receptor in pars reticulata indicates that D5-labeled axons may be originating from striatum and coursing through the striatonigral system. Apart from pars compacta of substantia nigra, the other major dopaminergic neurons are associated with hypothalamus. The localization of D5 receptor in hypothalamic arcuate nucleus suggests its role in the regulation of pituitary functions.

D5 receptor was found in both medium spiny GABAergic and large cholinergic interneurons in rat and human striatum, which is consistent with an earlier report in monkey brain. The stimulation of striatal GABAergic neurons appears to increase the release of GABA neurotransmitter from the axon terminals. However, the localization of the D5 receptor in cholinergic interneurons suggests a role of D5 receptor in modulation of axonal input as well as in release of acetylcholine from these neurons. The activation of dopamine D5 receptors in striatal cholinergic interneurons are shown to enhance the Zn2+ sensitive GABA_A currents, indicating the participation of the D5 receptor in modulating GABA neurotransmission. In electron microscopic studies, the observation that D5 receptor immunoreactive dendritic spines were predominantly making asymmetric synapses with axons provides further evidence of D5 receptor involvement in the modulation of incoming excitatory cortical information.

Another prominent dopaminergic target area is the cerebral cortex, where dopamine regulates both pyramidal and local circuit GABAergic neuronal functions. The mesocortical dopamine innervations to the prefrontal, cingulate and entorhinal cortices are involved in emotional, motivational and cognitive functions. Immunolabeling for D5 receptors was observed predominantly in layers IV–VI of the cerebral cortex, which is in agreement with other reports. In rat and human, the D5 receptor was mainly associated with pyramidal neurons and their dendrites. Dendritic spines of the cortical pyramidal cells are major postsynaptic targets of glutamatergic inputs. Dopamine terminals in the cortex predominantly make synapses on spines of pyramidal cells suggesting that these D5 receptor containing pyramidal neurons may interact with dopamine directly and modulate the excitability of neurons, similar to the D1 receptor.

The prominent species difference in D5 receptor labeling was observed in the hippocampal formation. In rat, receptors were concentrated in the neuronal cell body, whereas in human, reactivity was also associated with the dendritic fibres of neurons. Despite the discrepancies in earlier reports about the localization of D5 receptors in brain areas, all have reported that hippocampus is one of the areas where D5 receptor is dominantly expressed. The crucial role of the hippocampal dopaminergic system has been shown in several types of learning including passive avoidance, visual discrimination and positive reinforcement learning. Moreover, dopamine depletion in the hippocampus impairs spatial navigation. Several groups have shown that long-term potentiation (LTP), one form of the synaptic plasticity, is facilitated by the D1/D5 dopamine receptors. A recent demonstration of direct protein–protein interaction between dopamine D5 and GABA_A receptors in hippocampus suggests a novel mechanism for a D5 receptor role in the modulation of other receptor functions.

CONCLUSION

The localization of D5 receptors in the cortical, subcortical and limbic areas, where major dopaminergic innervation occurs, indicates that this receptor is probably involved in the enforcement of several physiological functions governed by the dopamine system. The D1-like (cumulative D1 and D5) receptors have been shown to be involved in several physiological functions including working memory, neural plasticity, early LTP, protein synthesis-dependent component of late LTP, and induction of gene expression. However, the individual contribution of D5 receptors in these functions is yet to be explored.

Acknowledgements—This study was supported by Spanish grants DGICYT (PB94-0219-C02), DGESIC (PM98-0225) and Junta de Andalucía (CTS-0161). We would like to extend our thanks to Maria José López-Alvarez for her assistance with the immunocytochemical experiments. During this research, Z. U. Khan has received fellowships from Junta de Andalucía, Universidad de Málaga and European Union BIOMED 1.

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(Accepted 6 June 2000)