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Distribution and Regulation of the G Protein-Coupled Receptor Gpr88 in the Striatum: Relevance to Parkinson's Disease

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1. Introduction

The human basal ganglia constitutes a functional neural network located at the base of the forebrain. It receives most of its afferent inputs through the striatum, the major nucleus of the basal ganglia accomplishing fast neurotransmitter-mediated operations through somatotopically organized projections to the principal neuron cell type, the striatal GABAergic spiny projection neurons. This spiny projection neurons, which make up 95 % of the neuron population of striatum (Kemp & Powell 1971), receive excitatory glutamatergic inputs from all areas of the cortex and specific thalamic nuclei (Gerfen & Wilson 1996; Bolam et al., 2000; Voorn et al., 2004; Doig et al., 2010), and also modulatory dopaminergic inputs from the substantia nigra pars compacta (Smith & Kieval 2000; Utter. & Basso 2008). Spiny Projection Neurons include two major subpopulations giving rise to the direct striato-nigral pathway, and the indirect striato-pallidal pathway which communicates information to the basal ganglia output structures; the internal segment of the globus pallidus and the substantia nigra pars reticulata (Smith, Y. & Kieval 2000; Gerfen & Wilson 1996). Although the two neuron subpopulations are GABAergic, they differ in a number of properties including the expression of different complements of dopamine, Adenosine, NMDA and acetylcholine receptor subtypes as well as of peptide content; the direct striato-nigral pathway neurons coexpress substance P and dynorphin, whereas the indirect striato-pallidal pathway neurons express enkephalin (Gerfen et al., 1990, 1991; Reiner & Anderson 1990; Gerfen & Wilson 1996; Le Moine & Bloch, 1995).

Based on the fact that striatal medium-spiny neurons are the major input targets and the major projection neurons of striatum, it is thought that integration of neurotransmission in these neurons is an important determinant of the functional organization of the striatum. Thus, changes in neurotransmission on striatal spiny projection neurons have been involved in the regulation of voluntary movement, behavioral control, cognitive function and reward mechanisms. For instance, massive spiny projection neuron loss and major dopamine

deficits in striatum lead to severe motor disorders, such as the excess of involuntary movements encountered in Huntington's disease and the rigidity and poverty of movements that typifies Parkinson's disease, respectively (Ross et al., 1997; Wolfgang & Stanley, 2003). Therefore, investigations addressed to characterize new receptor proteins displaying high densities and potential involvement in neurotransmission mechanisms within the striatum can provide new insight into the basal ganglia physiology and pathophysiology and also new clues for therapy of severe motor disorders.

A previous study reported a novel striatum-specific transcript, the strg/Gpr88, encoding an orphan G protein-coupled receptor of human and rodents (Mizushima et al., 2000). It displays highest sequence homology with 5HT1D and $\beta 3$ receptors. Since the original description, little data have been documented on the biological function(s) and the cellular and subcellular distribution of the Gpr88 protein. Hence, the Gpr88 endogenous putative ligand, the detailed Gpr88 protein distribution and GPR88 functional roles are unknown. One approach to gain functional insights into this novel gene coding for an orphan receptor is the precise analysis of its spatial and temporal expression to provide information about the neural morphological substrates supporting Gpr88 functions in the striatal complex.

Hence, the present findings provide *in situ* hybridization and light-level immunohistochemical evidence for Gpr88 localization in the rat and monkey striatum and its subcellular distribution in striatal neurons by using a validated polyclonal antibody specifically recognizing Gpr88, (Massart et al 2009). We also describe morphological data on the spatiotemporal Gpr88 expression in the developing rat striatum, suggesting that both nigrostriatal and corticostriatal pathways control its normal striatal pattern of expression. Using treatments with l-DOPA and dopamine antagonists, in unilateral 6-hydroxydopamine- and cortical ibotenate-lesioned rats, we further demonstrated that striatal Gpr88 expression is modulated by dopamine- and glutamate-regulated mechanisms involving trans-synaptic influences of the corticostriatal pathway input activity.

2. Widespread Gpr88 expression within the striatal complex

Using *in situ* hybridization and immunohistochemistry approaches, we demonstrated that Gpr88 mRNA and protein expression are specially abundant within restricted basal telencephalic structures including the dorsal striatum, nucleus accumbens, and olfactory tubercle and also in the inferior olivary complex (Fig. 1).

2.1 All striatal GABAergic spiny projection neurons express Gpr88

Gpr88 is expressed throughout the two anatomical and functional patch/striosome-matrix compartments in the rat and monkey striatal complex (Figures 1F, 2A) with higher receptor expression in patch/striosome than in the surrounding matrix compartment. The prevalence of Gpr88 in the patch/striosome compartment and also within the dorsolateral striatal sector, indicates that Gpr88 may play a central role in the modulation of both limbic and motor cortical-basal ganglia circuits (Ragsdale & Graybiel; 1988; Graybiel A.M., 1995; Gerfen & Wilson, 1996). Immunofluorescent stainings and double labelling *in situ* hybridization experiments demonstrated that Gpr88 is present in all the spiny projection neurons of both the direct striato-nigral pathway and the indirect striato-pallidal pathway (Figure 2 C,D).

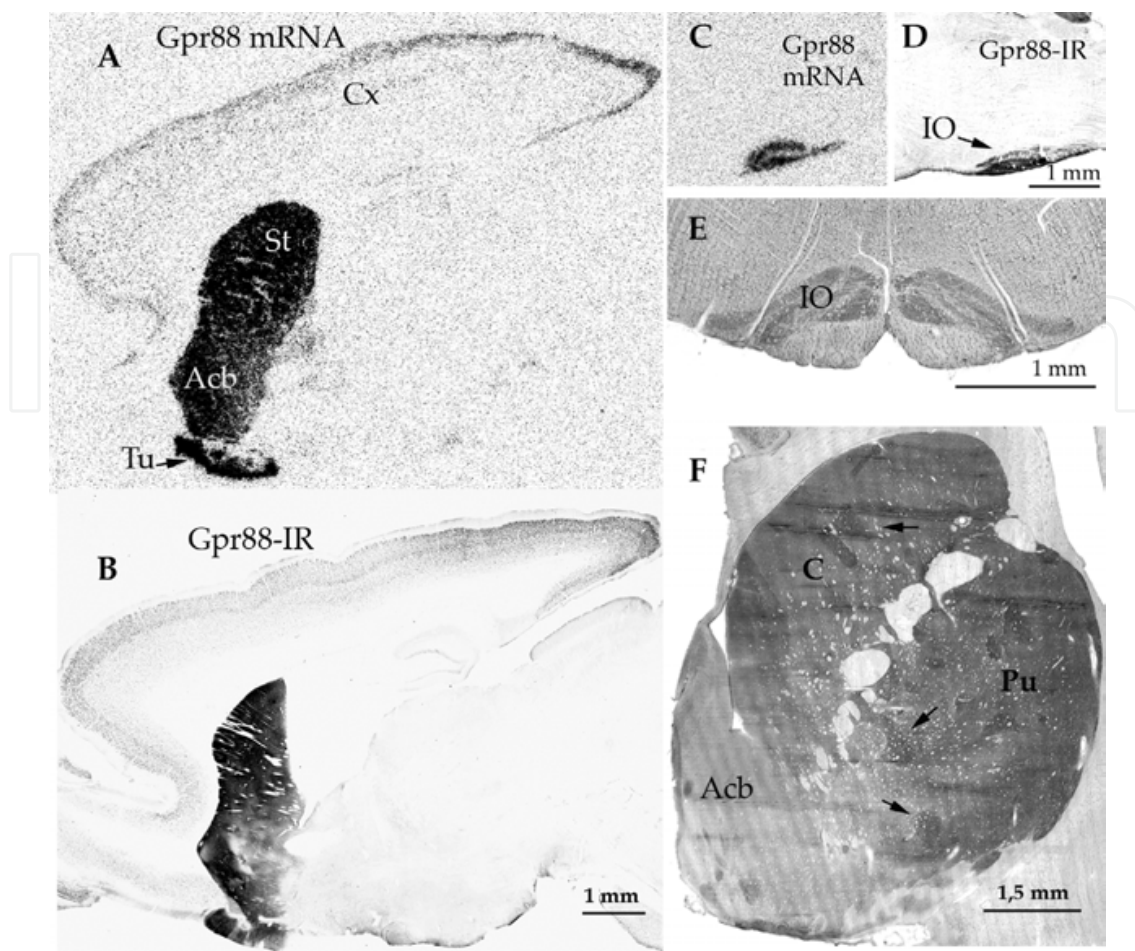


Fig. 1. Gpr88 distribution in the rat and the monkey brains. Both Gpr88 mRNA (A,C) and Gpr88 protein (B,D,E,F) are particularly concentrated throughout the striatum (St), nucleus accumbens (Acb), olfactory tubercle (Tu) and the inferior olive complex (IO) of the rat (A-E). Similar levels and distribution-pattern of Gpr88 immunoreactivity is detected in nucleus caudatus (C), putamen (Pu) and nucleus accumbens (Acb) of the monkey brain (F). Significant levels of Gpr88 are also present with a laminar distribution throughout the neocortex. Arrows in (F), point out small and intense Gpr88 stained areas corresponding to striosome striatal subcompartments. RT-QPCR data from rodents suggest that Gpr88 displays the highest expression levels compared to other known GPCRs of the striatum (Massart et al., 2007, 2008). The pattern of Gpr88 throughout the striatum of adult rats and monkeys is characterized by widespread distribution and regional differences (Figure 1), suggesting a central role of this orphan receptor in the modulation of sensorimotor related informations (Flaherty & Graybiel1994; Voorn et al., 2004). Although Gpr88 is prevalent in the striatal complex, we also detected moderate levels of both Gpr88 transcripts and protein throughout the cerebral neocortex (Figure 1A,B). Both signals display a similar non-homogeneous laminar distribution characterized by higher expression in the upper neocortical layers II-IV than in the lower layers V-VI. No Gpr88 expression was detected in the cortical layer I. Moreover, cortical Gpr88 expression represents about 20% of the GPR88 striatal expression, as assessed by different quantitative approaches including Western blot, immunohistochemistry and *in situ* hybridization. Double immuno-fluorescent labellings for Gpr88 and different neural cell-type specific markers have demonstrated that Gpr88 is an exclusive neuronal receptor of the brain, being absent from glial cells (Massart et al., 2009).

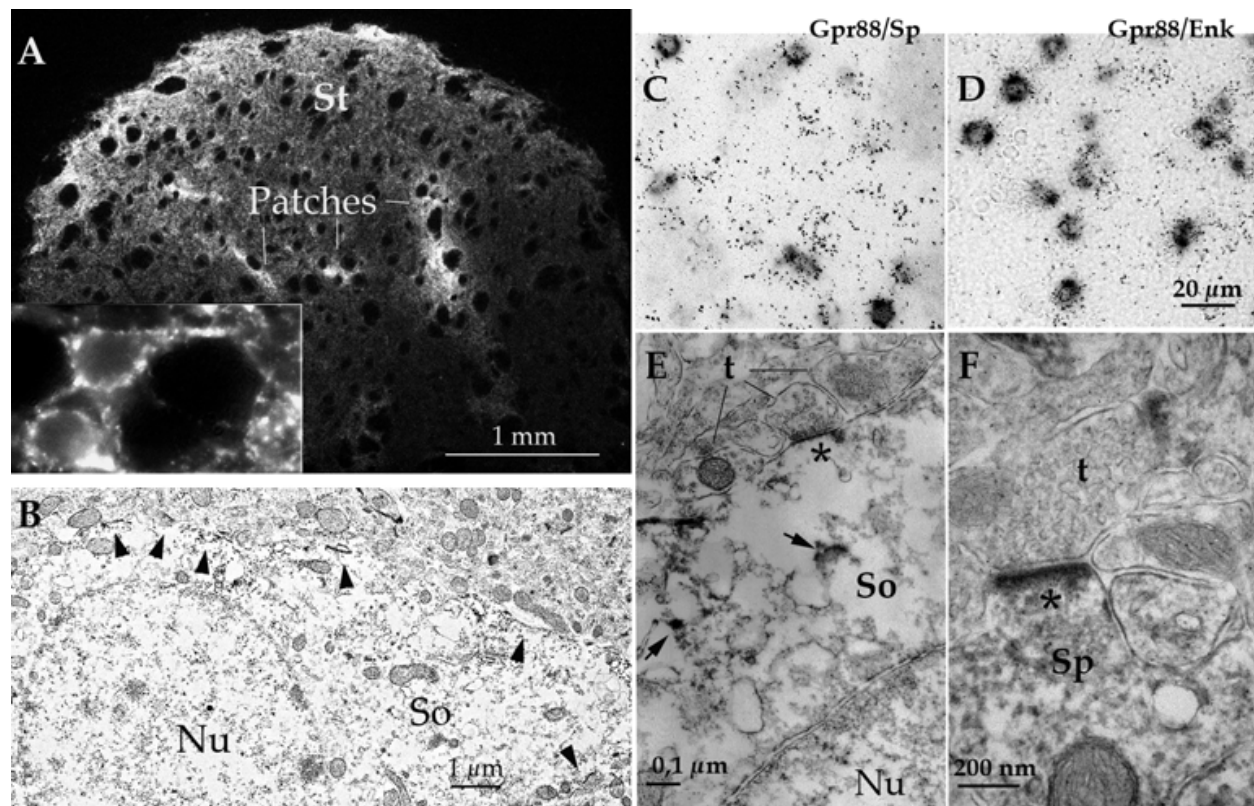


Fig. 2. Gpr88 distribution in the rat dorsal striatum. (A) The immunofluorescent Gpr88 signal is heterogeneously distributed within the dorsal striatum and characterized by its marked concentration in the striatal dorsolateral region and the patches compartments. The inset illustrates putative medium spiny neurons displaying intense Gpr88 labelling on the cell surface along the soma and dendrites. (C, D) double-labelling *in situ* hybridization indicates that all Substance P (dark-stained cells in C) and enkephalin (dark-stained cells in D) neurons, also express Gpr88 transcripts (detected by silver grain labellings). The distribution of the electron-dense immunoreactive reaction product, reflects the subcellular GPR88 presence in submembranous sites around the perikaryon (arrow-heads in B asterisk and arrows in E). The receptor is concentrated in symmetrical synapses in the cell body (asterisk in E) but also in asymmetrical synapses (asterisk in F) in dendritic spines (Sp). Note the absence of immunolabelling in synaptic contacts of two adjacent nerve terminals (t) in E. (Enk) Enkephalin, (Nu) Cell nucleus, (So) neuronal cell body, (Sp) Substance P in C, (Sp) dendritic spine in F.

Electron microscopic analysis of the Gpr88 immunolabelling in the rat dorsal striatum demonstrated a high proportion of electron dense Gpr88 positive dendritic spines, dendrite shafts and cell bodies (Figure 2 B,E,F) that are characteristic features of GABAergic spiny projection neurons (Somogyi et al., 1982; Bolam et al., 1983). However, no axonal or terminal Gpr88 immunolabeled profiles were observed. Likewise, globus pallidus and substantia nigra pars reticulata, two basal ganglia regions receiving the striato-pallidal and striato-nigral terminals respectively (Surmeier et al., 2007), lack Gpr88 immunoreactivity. All these morphological findings highlight a potential functional role for Gpr88 in synaptic events occurring on somatodendritic compartments and their integration in striato-nigral and striato-pallidal medium spiny neurons. Gpr88 immunoreactivity was often concentrated on discrete postsynaptic sub-membranous sites in a large proportion of asymmetrical (excitatory)

synapses that generally receive glutamate as neurotransmitter (Bouyer et al., 1984; Bolam et al., 2000) and also on symmetrical (inhibitory) synapses which could be supplied by terminals originating from GABAergic aspiny or cholinergic interneurons or even by intrastriatal GABAergic axon-collaterals from medium-spiny projection neurons. Double immunofluorescent labellings in the same section demonstrated no association between Gpr88 immunoreactivity and tyrosine hydroxylase immunolabelled axon-terminals. In contrast, the Gpr88 immunoreactive signal was often juxtaposed to most vesicular glutamate transporter1 immunoreactive terminals, indicating that Gpr88 is preferentially located on synapses supplied by cortical inputs, rather than by vesicular glutamate transporter2 immunoreactive thalamic inputs contacting medium spiny neurons (Herzog et al., 2001; Kaneko & Fujiyama, 2002; Freneau et al., 2004). Moreover, electron microscopy analysis demonstrates that Gpr88 immunoreactive signal is often present on the head of spines, where corticostriatal inputs mainly contact the dendritic tree of striatal spiny projection neurons (Bouyer et al., 1984; Dube et al., 1988; Ribak & Roberts 1990; Smith et al., 1994).

The preferential subcellular distribution of Gpr88 in striatal asymmetrical synapses of virtually all GABAergic projection neurons suggests a role for Gpr88 in the modulation of medium spiny neurons activity to cortical glutamatergic inputs and a potential role in the regulation of the flow of cortical information through the basal ganglia. Several lines of evidence indicate that cortical excitatory signals are modulated by dopaminergic synaptic contacts located on the neck of spines (Arbuthnott et al., 2000). Gpr88 location at specific synaptic sites, where corticostriatal and nigrostriatal afferents converge, further suggests involvement of Gpr88 in the modulation of both glutamatergic and dopaminergic signals received by the striatal medium spiny neurons.

3. Spatial and temporal Gpr88 expression in the developing rat striatum

To gain functional insights into striatal Gpr88 we have determined the profile of GPR88 expression in the prenatal and postnatal developing striatum of the rat by *in situ* hybridization and immunohistochemistry. Morphological data indicate that Gpr88 expression emerges with a homogeneous distribution, in the ventrolateral portion of the developing striatum at the embryonic day 16 (E16) of rat development (Figure 3A,B,C), a time when striatal neurons are both morphologically and functionally immature (van der Kooy & Fishell, 1987) and also when the patch-matrix striatal compartments, are not yet differentiated. The homogeneous Gpr88 mRNA distribution becomes heterogeneous when clusters of developing neurons displaying dense Gpr88 expression are seen throughout the dorsal and ventral striatal regions by the fetal stage E19-E20 (Figures 3D,E). Using double immunohistochemistry stained brain sections for Gpr88 and tyrosine hydroxylase, we confirmed that rich Gpr88 small areas strictly match the densely dopamine innervated striatal patch/striosome compartments (Gerfen et al., 1987). Levels of Gpr88 expression in patches compartments increase until the end of the first postnatal week and then decline in the second postnatal week with the ongoing development to eventually reach adult expression levels. Such developmental profile of Gpr88 expression in the prenatal and postnatal rat striatum suggests that the pattern of Gpr88 expression may be under the influence of afferent inputs reaching to the striatal primordia. This idea is based on the fact that the patchy-pattern profile of intense GPR88 expression in developing rat striatum closely matches the reported spatial and temporal development of the nigrostriatal dopamine afferents (Voorn et al., 1988), suggesting that the nigral dopamine inputs influence the patterning of striatal GPR88 expression. Such type of influence by the

dopamine inputs has been demonstrated for the establishment of the pattern of opiate receptors expression in the embryonic patch compartment (van der Kooy & Fishell, 1992). The cortical projections are the second major afferent input to the striatum that may act in concert with nigral dopamine inputs to guide development of striatal subcompartment phenotypes. For instance, studies in the monkey have shown the patchy distribution of corticostriatal afferents before the day of birth (Goldman-Rakic, 1981). Moreover, organotypic assays involving co-cultures of the striatum with substantia nigra or cortex indicate that afferents from these structures have a prominent influence on the development of striatal patch/matrix compartments (Snyder-Keller & Costantini 1996; Snyder-Keller et al., 2001; Snyder-Keller, 2004). The mutual influence of dopaminergic and glutamatergic pathways within the developing striatum is probably important for the setting up of striatal neurotransmission circuits, as previously shown by dopamine manipulations that influence corticostriatal synaptic configurations (Meshul & Tan, 1994; Meshul et al., 1999; Meshul & Allen, 2000; Avila-Costa et al., 2005). These observations support the idea that cortical glutamatergic inputs and/or dopamine glutamate interactions may exert a control on Gpr88 expression in the developing medium spiny neurons.

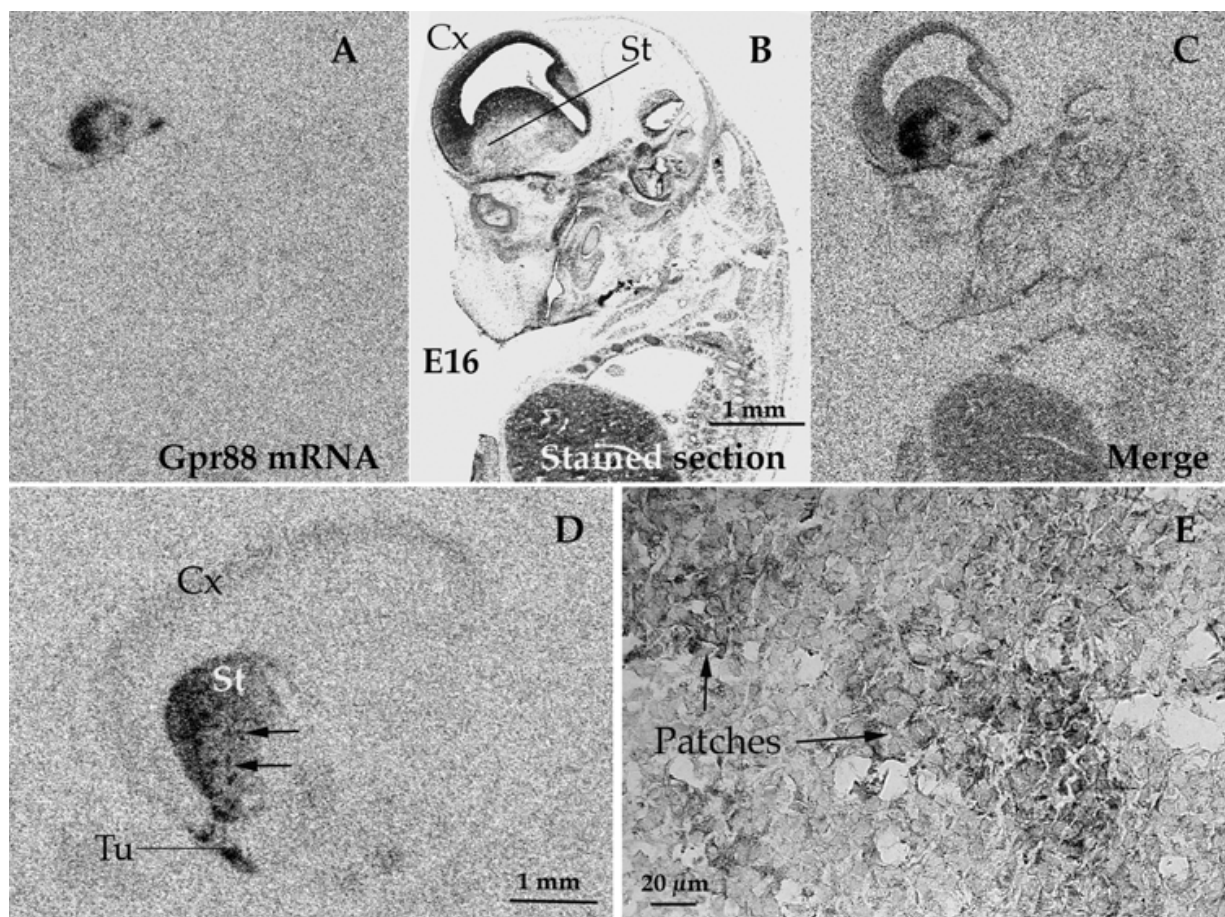


Fig. 3. Developmental profile of Gpr88 expression in the rat striatum. Gpr88 mRNA (A, D) and Gpr88-protein (E) expression in the developing striatum. (A) Homogeneous distribution of Gpr88 transcripts in the dorsolateral sector of differentiating striatum at E16. (D) Heterogeneous distribution of Gpr88-mRNA at E19. (F) Clusters of striatal developing neurons displaying dense Gpr88 immunoreactive signal (Gpr88-rich patches) at E20. (Cx) cortex, (St) striatum, (Tu) olfactory tubercle.

Although dopamine and glutamate afferents are the most likely candidates to modulate Gpr88 expression in developing medium-spiny projection neurons, other factors associated with nigral and cortical inputs may also play an important role in controlling Gpr88 expression within the striatal primordium. For instance, the nigrostriatal and corticostriatal pathways supply the striatum with brain-derived neurotrophic factor (BDNF) (Altar et al., 1997; Seroogy et al., 1994) which has been shown to influence survival, sprouting, and synaptogenesis in different neural systems (Hammond et al., 1999; Alsina et al., 2001; Mamounas et al., 2000). Moreover, studies in mature animals have shown that BDNF has profound effects on neurotransmission, activity-dependent synaptic remodeling, neurogenesis and receptors expression (Altar et al., 1997; Lessmann, 1998; Guillin et al., 2001; Tanaka et al., 2008; Taliaz, 2010). Rather than exclusive effects of either dopamine or glutamate on striatal Gpr88, continuous interplay among afferent signaling systems, including dopamine, glutamate and BDNF, is likely to refine the pattern expression of Gpr88 throughout the period of striatal development. Based on the spatiotemporal profile of GPR88 expression during striatal differentiation, we propose that the early receptor expression is modulated at least in part through a nigrostriatal and corticostriatal pathway dependent mechanisms. In support to the hypothesis of BDNF regulating Gpr88 expression during development, heterozygote BDNF-knockout mice have diminished Gpr88 mRNA levels in both the caude putamen and the shell of the nucleus accumbens (Massart et al., 2005).

4. Modulation of striatal Gpr88 expression by nigrostriatal and corticostriatal pathways in the rat in a model of Parkinson's disease

The demonstration of the regulation of striatal Gpr88 expression by nigrostriatal dopamine and cortical glutamate inputs was carried out in a rat model of Parkinson's disease (Schwartz & Huston 1996; Massart et al., 2009). Unilateral lesion of dopamine nigrostriatal pathway, caused by infusion of 6-OHDA in the medial forebrain bundle, produced a decrease in Gpr88 protein and mRNA expressions (Table 1). However, *in situ* hybridization analysis with double labelling showed that the effects of dopamine depletion were different in the two subpopulations of striatal medium spiny neurons. At the cellular level, 6-OHDA lesion induced a decrease in mRNA expression in striato-pallidal pathway neurons and inversely, a rise in striato-nigral projection neurons, in the dopamine depleted striatum (Table 1). Recently reported data (Heiman et al., 2008; Massart et al., 2009) showed that striatal Gpr88 mRNA expression is twice as high in striato-pallidal output neurons as in striato-nigral output neurons of rodents, the overall lesion-induced Gpr88 downregulation is consistent with the strong decrease in Gpr88 expression occurring in striato-pallidal pathway neurons, not compensated by the limited increase occurring in striato-nigral pathway neurons. These opposed variations are nearly completely reversed by a typical antiparkinsonian treatment with L-DOPA (Table 1).

Our finding revealed that D1 receptors, but not D2 receptors, activation exerts a positive influence on Gpr88 expression in the indirect striato-pallidal pathway of the dopamine-depleted hemisphere. On the contrary, D2 receptors stimulation controls Gpr88 expression in the direct striato-nigral pathway. This is rather surprising since D1 and D2 receptors are largely segregated to striatal neurons of the striato-nigral and striato-pallidal pathways, respectively (Gerfen et al., 1990; Le Moine & Bloch, 1995). In fact, in striato-pallidal medium spiny neurons harboring D2 receptors/Enk, in contrast to striato-nigral medium spiny

| | Treatment | Gpr88 protein – immunohistochemistry | | Gpr88 mRNA - <i>In situ</i> hybridization | | | | | |
|------------------|----------------------|--------------------------------------|------------|---|--------------|------------------|--------------|-------------------|--------------|
| | | | | Total mRNA | | mRNA / SP+ cells | | mRNA / ENK+ cells | |
| | | Intact | Lesioned | Intact | Lesioned | Intact | Lesioned | Intact | Lesioned |
| 6-OHDA lesion | Vehicle | 107 ± 3.8 | 91 ± 2.9 * | 69 ± 3.2 | 56 ± 1.4 * | 22 ± 1.4 | 29 ± 1.9 *** | 42 ± 2.1 | 31 ± 1.8 *** |
| | L- DOPA | 99 ± 5.1 | 90 ± 4.6 | 73 ± 4.2 | 70 ± 3.7 | 22 ± 1.4 | 26 ± 1.7 | 40 ± 0.8 | 38 ± 1.3 |
| | L-DOPA + SCH23390 | 108 ± 5.9 | 92 ± 5.6 | 76 ± 6.8 | 62 ± 3.2 | 23 ± 2.7 | 21 ± 1.6 | 43 ± 3.3 | 26 ± 4.3 *** |
| | L-DOPA + Haloperidol | 100 ± 5.5 | 92 ± 6.1 | 74 ± 4.4 | 75 ± 3.0 | 37 ± 1.9 *** | 26 ± 0.9 | 40 ± 1.4 | 39 ± 1.1 |
| Ibotenate lesion | Vehicle | 107 ± 3 | 83 ± 3 *** | 89 ± 3.8 | 78 ± 1.9 *** | 19 ± 0.5 | 17 ± 0.5 | 32 ± 0.9 | 23 ± 1.2 *** |

Table 1. Effects on Gpr88 expression of dopamine depletion, induced by unilateral 6-OHDA infusion into the medial forebrain bundle, or of a bilateral lesion of the cortex induced by multiple infusions of ibotenate. All data are expressed as group mean ±SEM. The raw data for 6-OHDA (nigro-striatal) lesion were analysed by two-way ANOVA with lesion and treatment as independent variable and the Bonferroni test for multiple comparisons was applied in post hoc analysis to determine which values were significantly different. For data from ibotenate-induced lesion, the Student’s unpaired two-tailed t-test was used to compare Ibotenate-injected vs. vehicle-injected rats. Alpha level level was set at 0.05. GraphPad 5 software (La Jolla, California, USA) was used to perform statistical analysis . * *P* < 0.05; ***P* < 0.01; ****P* < 0.001 vs. intact side (6-OHDA lesion) or intact, vehicle-infused animals (ibotenate lesion). See Massart et al. 2009 for details.

neurons containing D1 receptors/Sp, Gpr88 expression was downregulated by the 6-OHDA lesion and the reversion of this effect by l-DOPA was dependent on D1 receptor stimulation, as indicated by its blockade by the D1 receptor-selective antagonist SCH23390, but not by haloperidol, a D2 receptor-selective antagonist (Table 1). In parallel, in D1 receptor/Sp-expressing striato-nigral neurons, Gpr88 expression was upregulated by the lesion, in contrast to D2 receptor/Enk striato-pallidal output neurons. The reversion of this effect by l-DOPA was dependent of D2 receptors stimulation, as indicated by the absence of effects of SCH23390 (Table 1). Moreover, co-administration of l-DOPA and D2-receptor antagonist haloperidol raised Gpr88 expression in striato-nigral medium spiny neurons of the contralateral hemisphere (See Massart et al 2009; Taymans., 2005).

These results suggest that l-DOPA effects on Gpr88, in each of the two medium spiny neuron subsets, are not directly mediated by the respective dopamine receptor subtypes they express, but indirectly by dopamine receptor transmission through a different neurotransmitter afferent input to the medium spiny neurons. In particular l-DOPA and intrastriatal dopamine transmission can act as a neuromodulator of glutamate release in the dopamine depleted striatum (Jonkers et al., 2002; David et al., 2005; Stephens 2005). l-DOPA effects on Gpr88 expression in striato-pallidal pathway neurons are likely regulated through D1 receptor present on the soma and dendrites of excitatory corticostriatal projection neurons, leading to activation of the corticostriatal inputs. In contrast, l-DOPA/D2 receptors stimulation-induced Gpr88 decrease in striato-nigral neurons was probably mediated by reduced glutamate release from corticostriatal inputs by stimulation of presynaptic D2 receptors (Cepeda et al., 2001). Thus, l-DOPA-induced differential changes in Gpr88 levels

on both striato-nigral and striato-pallidal medium spiny neurons, may be mediated through dopamine-induced influences in corticostriatal glutamatergic neurotransmission mechanisms, as previously suggested for the modulation of other striatal markers expressed in these neurons (Uhl et al., 1988; Salin et al., 1997; Zeng et al., 2000; Blandini et al., 2003; Robelet et al 2004; Carta et al., 2005).

In support to the above hypothesis, corticostriatal deafferentation, elicited by ibotenate infusions, induced a marked Gpr88 mRNA and protein down-regulation in striato-pallidal neurons without significantly affecting Gpr88 in striato-nigral neurons (Table 1). These data agree with the involvement of corticostriatal glutamatergic input in the effects of dopamine depletion induced Gpr88 changes in the striatal medium spiny projections neurons, and with a greater influence of cortical inputs on Gpr88 expression in the striato-pallidal pathway neurons.

5. Conclusions

Gpr88 is an important constituent of the basal ganglia, being one of the most abundant GPCR in this brain region. Although its function is unknown, detailed analysis of its gene expression in striatal spiny projection neurons suggests that Gpr88 has typical features of a GPCR in charge of transducing extracellular signals. First, it is expressed at the plasma membrane of striatal medium-spiny projection neurons, and probably exposed to the extracellular signals. Second, establishment of Gpr88 expression during development is concomitant with major dopaminergic and glutamatergic afferences reaching the embryonic striatum. Third, Gpr88 expression is enriched in the patch/striosome compartment, which suggests its involvement in the modulation of both limbic and motor cortical-basal ganglia circuits. Fourth, Gpr88 expression is influenced by modifications of cortical and nigral inputs to medium spiny neurons occurring in a situation modeling the pronounced loss of dopamine-producing neurons, occurring in Parkinson's disease.

Striato-nigral and striato-pallidal pathways neurons play an important role in integrating circuits of the basal ganglia/basal forebrain and finding on new proteins in these two major striatal output pathways, may contribute to a better understanding of certain pathophysiologic states (e.g., movement and psychiatric disorders). Hence, the rich and selective expression of GPR88 in the two striatal subpopulations medium-spiny projection neurons, directly receiving dopaminergic and glutamatergic inputs provides an anatomical basis for potential therapeutic applications, particularly in the striatum where modulation of glutamatergic and dopaminergic functions have important consequences for Parkinson's disease and its treatment.

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Mechanisms in Parkinson's Disease - Models and Treatments

Edited by Dr. Juliana Dushanova

ISBN 978-953-307-876-2

Hard cover, 582 pages

Publisher InTech

Published online 08, February, 2012

Published in print edition February, 2012

Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

How to reference

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Renaud Massart, Pierre Sokoloff and Jorge Diaz (2012). Distribution and Regulation of the G Protein- Coupled Receptor Gpr88 in the Striatum: Relevance to Parkinson's Disease, Mechanisms in Parkinson's Disease - Models and Treatments, Dr. Juliana Dushanova (Ed.), ISBN: 978-953-307-876-2, InTech, Available from: <http://www.intechopen.com/books/mechanisms-in-parkinson-s-disease-models-and-treatments/distribution-and-regulation-of-the-g-protein-coupled-receptor-gpr88-in-striatum>

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