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REVIEW ARTICLE

The Modulation of Pain by Metabotropic Glutamate Receptors 7 and 8 in the Dorsal Striatum

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Abstract: The dorsal striatum, apart from controlling voluntary movement, displays a recently demonstrated pain inhibition. It is connected to the descending pain modulatory system and in particular to the rostral ventromedial medulla through the medullary dorsal reticular nucleus. Diseases of the basal ganglia, such as Parkinson's disease, in addition to being characterized by motor disorders, are associated with pain and hyperactivation of the excitatory transmission. A way to counteract glutamatergic hyperactivation is through the activation of group III metabotropic glutamate receptors (mGluRs), which are located on presynaptic terminals inhibiting neurotransmitter release. So far the mGluRs of group III have been the least investigated, owing to a lack of selective tools. More recently, selective ligands for each mGluR of group III, in particular positive and negative allosteric modulators, have been developed and the role of each subtype is starting to emerge. The neuroprotective potential of group III mGluRs in pathological conditions, such as those characterized by elevate glutamate, has been recently shown. In the dorsal striatum, mGluR7 and mGluR8 are located at glutamatergic corticostriatal terminals and their stimulation inhibits pain in pathological conditions such as neuropathic pain. The two receptors in the dorsal striatum have instead a different role in pain control in normal conditions. This review will discuss recent results focusing on the contribution of mGluR7 and mGluR8 in the dorsal striatal control of pain. The role of mGluR4, whose antiparkinsonian activity is widely reported, will also be addressed.

Keywords: mGluR7, mGluR8, dorsal striatum, chronic pain, descending pain modulatory system, hyperglutamatergism.

1. INTRODUCTION

The dorsal striatum is part of basal ganglia, a set of brain structures controlling voluntary movement [1-3]. Diseases affecting dorsal striatum lead to disturbances of movement and muscle tone [4-10]. Apart from motor control, growing evidence suggests a role of dorsal striatum in cognition [11], extinction [12], addiction [13], reward and decision making [14] and somatosensory functions [15, 16]. The dorsal striatum is activated by noxious stimulation [15, 17-21] and the electrical or chemical stimulation of the striatum inhibits pain [22-25]. The fact that in dorsal striatum diseases such as Parkinson' and Huntington's diseases almost half of the patients complain of pain, confirms the role of the dorsal striatum in mediating analgesia [26-28]. In fact, dorsal striatum is characterized by a large concentration of opiates and cannabinoids [29-31], neurotransmitters of the endogenous analgesic system. The pain inhibition by dorsal striatum passes through the activation of the descending pain modulatory system and in particular, involves the rostroventromedial medulla (RVM) [24, 32, 33]. The point of convergence between the dorsal striatum and the descending pain modulatory system lies in the medullary dorsal reticular nucleus, a pronociceptive area, projecting in turn to the dorsal horn of the spinal cord [34] (Fig. **1**). Increased glutamate transmission in the basal ganglia output nuclei contributes to the pathogenesis of Parkinson's disease [35]. Increased glutamate transmission is also associated with pain sensitization, a key mechanism associated with pain chronicization [36]. A way to counteract glutamate hyperactivity associated with both, chronic pain or neurodegenerative disorders, is throughout the inhibition of ionotropic glutamate receptors (iGluRs) and group I metabotropic glutamate receptors (mGluRs) or the activation of group II and III mGluRs. Within the group III, apart from mGluR6 whose expression is limited to the retina [37], mGluR4, mGluR7 and mGluR8 are found on excitatory corticostriatal terminals and GABAergic output terminals of the basal ganglia [38]. Since group III mGluRs negatively control neurotransmitter release [39], drugs which selectively stimulate these receptors may prove useful in chronic pain and neurodegenerative disorders. Moreover, in light of recent development of novel se-

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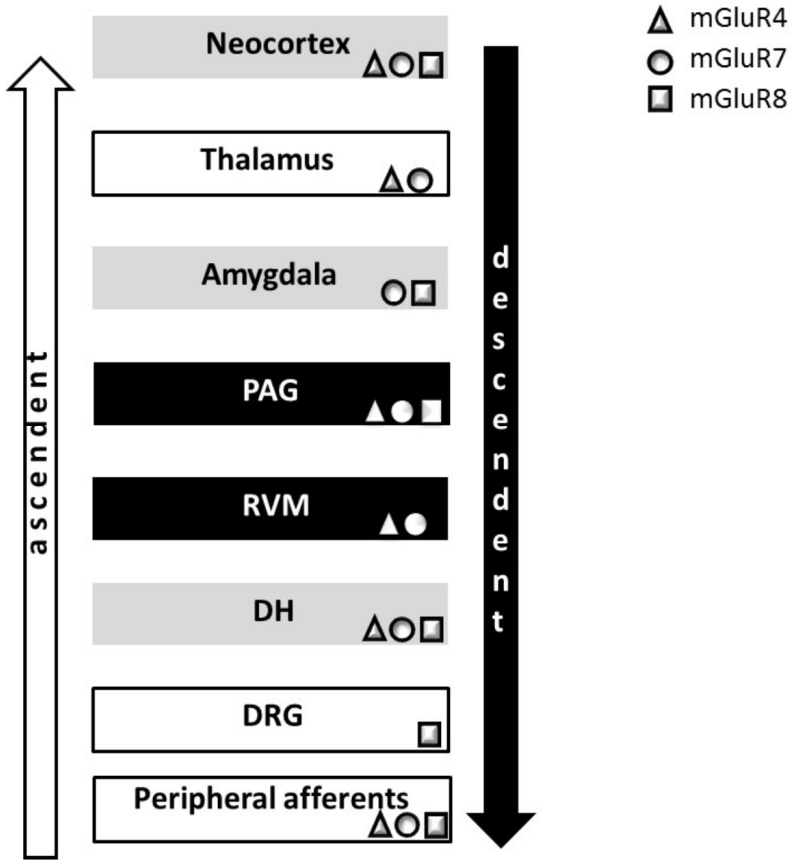

Fig. (1). Schematic representation of the expression of mGluRs of group III within the ascending (white) and descending (black) pain pathways. Areas which are common to the two pathways are represented in grey. With the exception of mGluR6 that is confined to the retina, the other mGluR subtypes of group III are expressed in the peripheral, spinal and supraspinal structures of the pain neuraxis where they modulate responses to pain. PAG, periaqueductal grey; RVM, rostral ventromedial medulla; DH, dorsal horn; DRG, dorsal root ganglia.

lective and brain-penetrating compounds targeting each subtype of group III mGluRs [40, 41], the neuroprotective potential of mGluR4, mGluR7 and mGluR8 is beginning to emerge.

2. mGluR4

The highest expression of mGluR4 has been found in the cerebellar cortex, thalamus, hippocampus and basal ganglia [42, 43] (Figs. **1** and **2**). mGluR4 is also expressed in the amygdala [44] and olfactory bulb [45]. Within the basal ganglia, the expression of mGluR4 has been found on glutamatergic corticostriatal and GABAergic striatopallidal and striatonigral terminals (Fig. **2**) [42-43]. Apart from CNS mGluR4 is also expressed in peripheral tissues such as gastrointestinal tract [46, 47], cervix, urinary bladder [48, 49], pancreatic islet cells [50] and in adrenal medullary ganglion cells [51]. mGluR4 is also highly expressed in cells of the immune system [52, 53]. A single isoform for mGluR4, mGlu4b, with a longer and different C-terminal domain has been identified in both, humans and rodents [54]. Like all the mGluRs, mGluR4 is organized in homodimers and heterodimers, such as that with mGluR2 [45]. Like the other mGluRs of group III, mGluR4 receptor is mainly localized at the presynaptic level and functions as an autoreceptor or heteroreceptor inhibiting glutamate and GABA release, respectively. The first evidence about the role of mGluR4 came from the mGluR4 knock-out mice which showed motor [55, 56] and memory retention [57] impairments, lack of motor stimulant effect of ethanol [58] and increased anxiety–like behavior [56]. Orthosteric agonists such as L-(+)-2-amino-4-phosphonobutyric acid, L-AP4, (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid, ACPT-1, (2S)-2-amino-4-[hydroxy[hydroxy(4-hydroxy-3-methoxy-5-nitrophenyl)methyl]phosphoryl]butanoic acid, LSP1-2111 and (2S)-2-amino-4-({[4-(carboxymethoxy)phenyl](hydroxy) methyl}(hydroxy)phosphorryl) butanoic acid, LSP4-2022, display poor CNS permeability and selectivity [59]. Among these, LSP1-2111, showed a higher selectivity at mGluR4 over mGluR8 and mGluR7 and when administered in mice proved to have anxiolytic- and antischizophrenic-like effects [60, 61], whereas the LSP4-2022, which displays a higher potency, proved to play antiparkinsonian, antipsychotic, analgesic and pro-depressant effects [62-65]. Selectivity to the mGluR4 was achieved through the synthesis of compounds binding the allosteric site of the transmembrane domain. The N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide, PHCCC, was disclosed as a selective mGluR4 PAM and mGluR1 antagonist [66] and showed antiparkinsonian effects in rodent models of Parkinson's disease [67]. Other more selective mGluR4 PAMs were synthesized later,

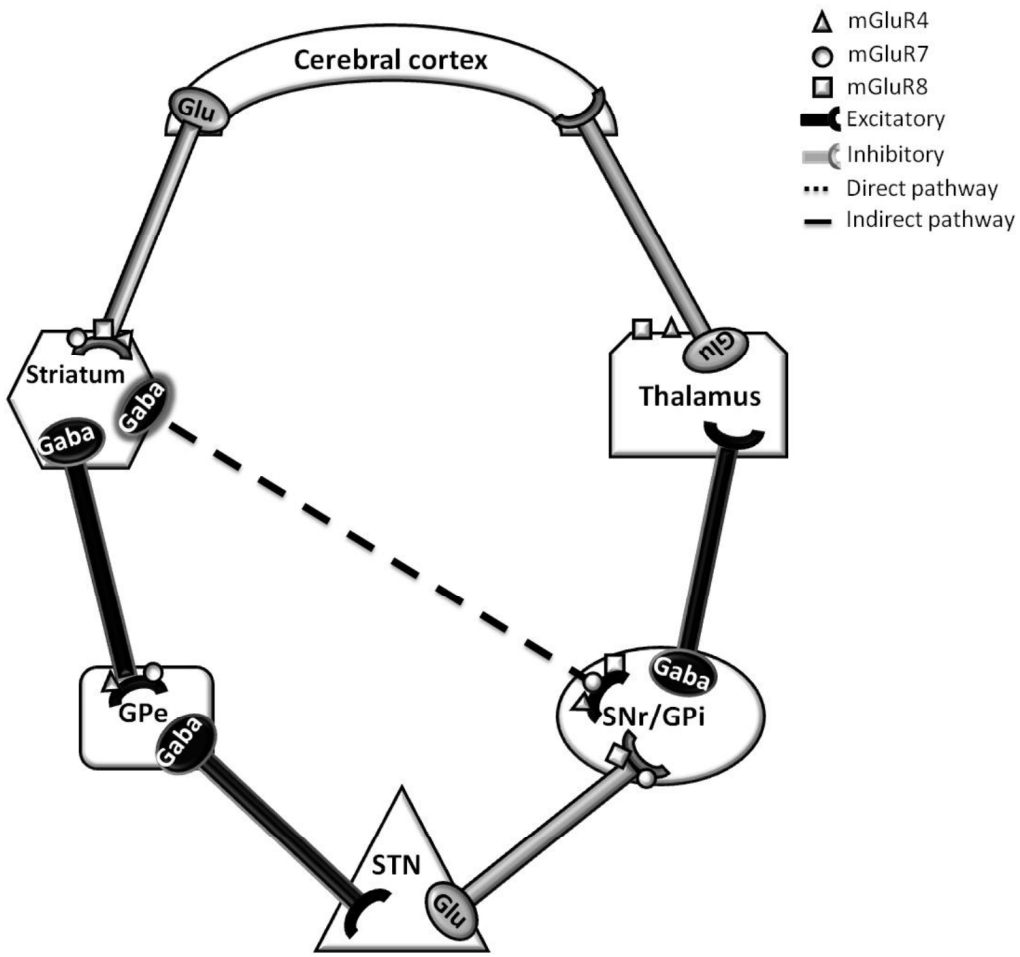

Fig. (2). Graphical representation of the expression of group III mGluR subtypes (mGluR4, mGluR7 and mGluR8) within the basal ganglia direct and indirect pathways. The cerebral cortex sends excitatory projections to the dorsal striatum, which in turn sends inhibitory projections which form two parallel pathways: the direct and indirect one. In the direct pathway, dorsal striatum sends inhibitory projections straight to the interal globus pallidus (GPi)/substantia nigra pars reticulata (SNr). In the indirect pathway, dorsal striatum sends inhibitory projections to the external globus pallidus (GPe), and hence to the subthalamic nucleus, which in turn sends excitatory projections to the GPi/SNr. This latter in turn sends inhibitory projections to the thalamus that finally comes back to the cortex through excitatory inputs. The distribution of group III mGluRs is represented by placing different symbols for each mGluR subtypes on axon terminals: triangle (mGluR4), circle (mGluR7) and square (mGluR8).

such as the (6E)-6-(hydroxyimino)-N-(pyridin-2-yl)-2-oxatricyclo [5.4.0.0^{3,5}]undeca-1(11),7,9-triene-3-carboxamide, VU0359516, (1S,2R)-N1-(3,4-dichlorophenyl)cyclohexane-1,2-dicarbo-xamide, Lu AF21934, the N-(3-chloro-4-fluorophenyl)-1H-pyrazolo[4,3-b]pyridin-3-amine, VU0418506, the cis-2-[[(3,5-dichloro-phenyl)amino]carbonyl]cyclohexane-carboxylic acid, VU0155041, the 3-amino-pyridine-2-carboxylic acid [3-chloro-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenyl]-amide, VU0477886, the 5-methyl-N-(4-[(11)C]methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2-amine ([(11)C], ADX88178, and the foliglurax, these last two combining high mGluR4 selectivity and excellent pharmacokinetic properties [68, 69]. Selective mGluR4 PAMs proved to ameliorate both, Parkinson's disease motor impairments and levodopa-induced dyskinesia [70-73]. This evidence has been so striking to start up clinical trials with foliglurax, which have shown to be safe and well tolerated, endowed with optimal pharmacokinetic properties and effective against levodopa-induced end-of-dose, wearing off and dyskinesia drawbacks. In addition to their proven efficacy in Parkinson's disease, selective mGluR4 PAMs have shown to be effective against positive, negative and cognitive symptoms of schizophrenia [74], anxiety [75, 76], drug addiction [58, 77, 78], hyperalgesia [79, 80], experimental autoimmune encephalomyelitis [52], multiple sclerosis [53] and generally in neuroinflammation-based diseases [81, 82]. In addition to neuropsychiatric diseases, mGluR4 PAMs proved to be protective also in esophageal and gastrointestinal disorders [83, 84]. Despite the broad-spectrum beneficial effects on CNS, immune and gastrointestinal diseases, stimulation of the mGluR4 receptor has also shown lowering the epileptic threshold. The injection of PHCCC enhanced absence-like seizures in wild type mice treated with pentilenetetrazol, whereas it was totally inactive in mGluR4 knockout mice, which were intrinsically resistant to pentylenetetrazol [85].

2.1. mGluR4 and Basal Ganglia

The expression of mGluR4 has been found on corticostriatal glutamatergic terminals [38, 42, 43], striatopallidal and striatonigral GABAergic terminals [38, 43] and on glutamatergic terminals originating from the STN and projecting to the SNr [38, 43] (Fig. **2**). In the corticostriatal glutamatergic terminals, mGluR4 stimulation decreases glutamate release [86-89] and the excitatory transmission from the cortex [86-88]. In particular, mGluR4 is predominantly localized on the glutamatergic corticostriatal terminals, targeting the indirect pathway [90], whose hyperactivity in Parkinson's disease has been widely reported [91-94]. In this context, due to its inhibitory action on glutamate transmission, the activation of mGluR4 may restore the balance between the direct and indirect pathways of the basal ganglia and exert antiparkinsonian activity. Indeed, the administration of a group III agonist with preferential action on mGluR4 at this level improved akinesia in rats with a 6-OHDA-induced lesion of SNr [86]. At striatopallidal level, mGluR4 inhibited glutamate and GABA release [45, 67, 95-97], reversed dopamine denervation-induced akinesia [98] and proved to be neuroprotective in MPTP-exposed rats [99]. Thus, the downregulation of the striatopallidal pathway may be another action through which the activation of mGluR4 could mediate antiparkinsonian effect. As for striatopallidal, also the striatonigral activation of mGluR4 relieved reserpine-induced akinesia [100]. Moreover, it has been shown that the activation of group III mGluRs into the SNr reduced NMDA toxicity in wild type mice though not in mGluR4 knock-out mice, and that the selective stimulation of mGluR4 within the SNr by VU0155041 provided neuroprotection against 6-OHDA lesion as well as significant preservation of motor function [101] showing that mGluR4 is neuroprotective against SN dopaminergic neuron death [102]. Thus, activation of mGluR4 in sites of basal ganglia which are hyperactive in Parkinson's disease is expected to inhibit the indirect pathway, while preserving the excitation of the direct pathway, thereby normalizing basal ganglia output. Consistently, mGluR4 PAMs by restoring the balance between the direct and indirect pathways proved effective against the motor symptoms of Parkinson's disease.

2.2. mGluR4 and Pain

mGluR4 proved to be expressed all along the pain neuraxis: peripheral terminals [103], dorsal root ganglia, dorsal horn of the spinal cord (Fig. **1**) [63, 104, 105] and supraspinally within the amygdala [44], thalamus [45] and input/output striatum fibers (Figs. **1** and **2**) [38, 42, 43]. The contribution of mGluR4 on pain modulation came from the evidence that the mGluR4 knock-out mice showed increased nocifensive responses in the second phase of formalin test, thus the lack of mGluR4 appears to increase the development of inflammatory pain [63]. Consistently, the systemic administration of LSP4-2022, a mGluR4 selective orthosteric agonist, alleviated inflammatory and neuropathic pain-induced mechanical hypersensitivity [63]. The contribution of spinal mGluR4 in nociceptive processing has been highlighted by several studies in both, healthy or chronic pain conditions. The intrathecal administration of mGluR4 agonists or PAMs, reduced hypersensitivity induced by inflammatory or neuropathic pain models [63, 106]. The involvement of mGluR4 in reducing pain hypersensitivity was demonstrated by the fact that the effect of LSP4-2022 in alleviating pain hypersensitivity was reduced by 78% in mGluR4 knock-out mice [63] and was blocked by a photoswitchable mGluR4 negative allosteric modulator, NAM [80]. Interestingly, mGluR4 activators were devoid of activity on acute pain threshold in healthy rodents [63, 106]. Accordingly, the spinal administration of VU0155041, a mGluR4 PAM, dose-dependently attenuated hyperalgesia in neuropathic rats. Furthermore, mGluR4 expression was downregulated in the dorsal horn of the spinal cord in neuropathic rats [107] suggesting that the downregulation of the spinal mGluR4 expression contributes to the development of hyperalgesia in neuropathic pain conditions [107]. The role of mGluR4 at spinal level seems to be well defined, while its downregulation is associated with a hypersensitivity to pain, its stimulation produces pain inhibition solely in conditions of chronic pain, in instances where glutamatergic transmission is over-activated.

2.3. mGluR4 and Dorsal Striatum

Despite the ascertained importance of mGluR4 in pain control at the spinal level, the only study investigating the role of mGluR4 at supraspinal level failed to found any effect of mGluR4. Indeed, when the mGluR4 PAM, VU015504, was locally microinjected into the dorsal striatum in sham and neuropathic rats it failed to change the tail flick latency or activity of the ON and OFF cells of the RVM [32].

3. mGluR7

Among all mGluRs, mGluR7 is the one showing the widest expression in the central nervous system (CNS). Striatum, hippocampus, thalamus and neocortex are the brain structures with the highest density of mGluR7 expression [108-110]. Among the 15 existing variants of the mGluR7, the mGluR7a and mGlu7Rb isoforms, whose difference lies in the C-terminal domain, are the most widespread in the CNS [38, 59, 108, 111]. The other isoforms of the receptor have been observed at the peripheral level in tissues such as the testis, trachea, uterus, and salivary glands [112]. As the other mGluRs of group III, mGluR7 is mainly located at the presynaptic active zone of glutamatergic and GABAergic terminals [95, 109, 113]. This receptor serves as an auto- or hetero-receptor, whose activation inhibits the release of endogenous neurotransmitters, glutamate or GABA, respectively [39, 114-117]. The low affinity for glutamate characterizes mGluR7. As a direct consequence of its low affinity, mGluR7 is activated only under high concentrations of the neurotransmitter [117], such as that observed in neuropathological conditions. So far the potential of mGluR7 in neuroprotection against "*hyperglutamatergism*" underlying neurodegenerative and neuropsychiatric diseases has been scarcely explored due to the lack of selective and brain permeable agents. In the absence of selective ligands, the first studies related to the role of mGluR7 were those using mGluR7 knock-out mice strategies. These mice showed anxiolytic-like phenotype [118, 119], alteration in fear-induced responses [120] and impairment in cognitive performance [121, 122]. The N,N'-dibenzhydrylethane-1,2-diamine dihy-

drochloride, AMN082, a potent (EC50 = 260 nM) and brain-penetrating mGluR7 selective allosteric activator, has been identified by Mitzukawa *et al*. in 2005 [123]. AMN082, when systemically administered, produced antidepressant- and anxiolytic-like effects, this latter being in contrast with the phenotype of mGluR7 knock-out mice [79, 124-127]. AMN082 facilitated also MK-801-induced pro-psychotic effects [60], reduced motor deficits in several Parkinson's disease models [128, 129], inhibited cocaine, heroin and ethanol self-administration [130-132], impaired motor performance [133] and displayed mixed anti- and pro-convulsant effects [134]. The selectivity of AMN082 for mGluR7 has been reconsidered since an off-target action, the blockade of noradrenaline and serotonin transporters by a metabolite produced *in vivo* [135, 136], has emerged.

3.1. mGluR7 NAMs

Fortunately, successively NAMs of mGluR7 have been developed allowing the characterization of its role in normal and pathological states. The 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one, XAP044, is a selective mGluR7 antagonist (IC50 = 5.5 mM) which binds the venus fly trap (VFD) domain of mGluR7. It has shown anxiolytic and antidepressant effects [137]. 6-(4-methoxyphenyl)-5-methyl-3-pyridin4-ylisoxazolo[4,5-c]pyridin-4(5H)-one, MMPIP, is a selective mGluR7 NAM [138] which has shown to impair cognition, social interaction and to increase the time of immobility in the tail suspension, an effect that corresponds to a pro-depressive activity, in healthy rodents [126, 139]. MMPIP has also shown antipsychotic effect in animal models of schizophrenia [140] and analgesic, antidepressant, anxiolytic and pro-cognitive effects in those of neuropathic pain [141]. The 6-(2,4-dimethylphenyl)-2-ethyl-6,7-dihydro-4(5H)-benzoxazolone, ADX71743, is another selective mGluR7 NAM (IC50 of 63/88 nM at human and rat mGluR7, respectively), which has shown anxiolytic-like effect without producing motor impairment. ADX71743 did not instead show an antidepressant-like effect [142]. Recently, ADX71743 has also shown antipsychotic activity in rodent models of schizophrenia [141]. The specificity of the effect of ADX71743 and MMPIP was assessed throughout electrophysiology experiments in the motor cortex in which the two NAMs increased the amplitude of the field potentials in wild type though not in mGluR7 knock-out mice [141]. AMN082 is not the best tool to clarify the role of mGluR7, as it rapidly induces internalization behaving paradoxically as a mGluR7 blocker [143] and it is not selective *in vivo* [135]. All that could be the reason for the discrepancy of results obtained and the mismatch with the phenotype of mGluR7 knock-out mice, which inherently presents the limit of adaptation to the lack of the protein during the development. In this regard, the introduction of mGluR7 NAMs marked a big step forward to define an unequivocal role for the mGluR7.

3.2. mGluR7 and Basal Ganglia

The expression of mGluR7 within the basal ganglia shows the highest density in the striatum and SNr [38, 110] (Fig. **2**). Both the striatum and SNr receive excitatory projections from the cortex and subthalamic nucleus, respectively. In Parkinson's disease, the degeneration of nigrostriatal dopaminergic neurons causes hyperactivation of glutamate transmission on corticostriatal [144, 145] and the subthalamic nucleus (STN) [146-148] projections. "*Hyperglutamatergism*" represents a critical event in Parkinson's disease leading to neuron death and motor disability [149-151]. In the striatum, the stimulation of mGluR7 has shown to strategically reduce the glutamatergic tone and attenuate cholinergic interneuron hyperactivation [152-154]. Consistently, the oral or intrastriatal administration of AMN082 blocked the haloperidol-induced catalepsy [128, 129]. The systemic administration of AMN082 reduced apomorphine-induced rotations in a Parkinsons's disease model induced by the unilateral injection of 6-OHDA [128]. AMN082 also reversed haloperidol-induced catalepsy when given orally, into the striatum or SNr [128, 129]. Interestingly, the effective intrastriatal dose of AMN082 was tenfold lower than that effective in the SNr [129] and the anti-dyskinetic effect was observed in wild type though not in mGluR7 knock-out mice [128]. The efficacy of AMN082 in ameliorating motor symptoms in animal models of Parkinson's disease may be associated with a rebalance of the overactive excitatory neurotransmission on corticostriatal terminals of the basal ganglia. In this context, the abundance of mGluR7 at this level offers a suitable target for curbing glutamate elevation [38, 110]. Apart from glutamatergic cortical and subthalamic nucleus terminals, mGluR7 is also expressed at GABAergic striatopallidal and striatonigral projections [38, 42, 43, 155] (Fig. **2**). Presynaptic activation of group III mGluRs by broad-spectrum agonists in the globus pallidus and SNr reduced motor impairments in Parkinson's disease models [156-160], however the contribution of mGluR7 in this effect is unlikely, due to the weak affinity of the ligands used towards mGluR7 [158, 161] and the fact that when administered in the SNr, AMN082 induced a weak antiparkinsonian activity [100].

3.3. mGluR7 and Pain

The expression of mGluR7 within pain modulating areas is shown in Fig. **1**. The systemic administration of AMN082 has shown to both, facilitate [162] or inhibit pain responses [163]. Moreover, AMN082 potentiated the analgesic effect of morphine or glial inhibitors [163, 164]. When intrathecally administered, AMN082 reduced mechanical allodynia and thermal hyperalgesia induced by the injection of carrageenan or incision of the hind paw [165]. Intrathecal AMN082 also attenuated nocifensive responses and mechanical hyperalgesia after the intradermal injection of formalin into the forelimbs of sheep [166]. The intrathecal administration of AMN082 has not instead affected hyperalgesia in neuropathic rats [107]. When administered into the ventrolateral periacqueductal grey, VL PAG, AMN082 instead facilitated nociception in healthy rats [167, 168] and, consistently, increased the activity of pain responding "pro-nociceptive" ON cells and inhibited that of "antinociceptive" OFF cells of the RVM [168]. It has been also found that the stimulation of mGluR7 in the PAG inhibited glutamate release [168]. Thus, pain facilitation could be attributable to the inhibition of the descending pain modulatory system [169]. A facilitatory effect on pain by AMN082 has been also found in the central nucleus of amygdala (CeA). The

perfusion with AMN082 into the CeA by reverse microdialysis decreased spinal withdrawal reflex threshold in healthy rats whereas it was devoid of activity in arthritic rats [170]. However, this lack of effect of AMN082 in pathological conditions is just the opposite to what has been found for mGluRs of group III, the modulation of which is effective only during chronic pain conditions [32, 33, 141, 170-176]. Differently, from the PAG and CeA, AMN082 locally administered into the nucleus tractus solitarius, NTS, inhibited cardiac nociception induced by pericardial capsaicin in rats [177]. This effect was blocked by both, a broad-spectrum group III antagonist, (RS)-α-methylserine-O-phosphate, M-SOP, or vagal deafferentation, thus suggesting that mGluR7-induced decrease in glutamate release may impair nociceptive transmission from the NTS to the spinal cord [177]. AMN082 also produced antinociception when locally administered in the nucleus accumbens [178]. All these studies put together are not able to define an unique role of the mGluR7 on the modulation of pain, suggesting that it is site- and condition (healthy versus pathological)- dependent. Again AMN082 is not the most suitable compound to investigate the role of mGluR7 owing to its off-target effects [135] and the rapid internalization it causes [143].

3.3.1. Effects of mGluR7 NAMs

MMPIP, a selective mGluR7 NAM, systemically administered, was able to ameliorate sensory, affective and cognitive impairments in neuropathic mice whereas it was devoid of activity in control mice [141]. Another mGluR7 NAM, ADX71743, reduced visceral pain behavior, increased the threshold of visceral sensitivity and reduced anxiety behavior in a stress-sensitivity rat strain [179]. When MMPIP was intra-VL PAG administered it inhibited pain responses in formalin and neuropathic pain models whereas it was devoid of activity in healthy rodents [180]. In neuropathic rats, MMPIP also decreased the activity of the ON cells and increased that of the OFF cells in the RVM, consistently with pain inhibition [180]. The administration of MMPIP in the hippocampus decreased the activity of pain-excited neurons and increased that of pain-inhibited neurons [181]. So while for AMN082 there are contrasting effects that vary depending on the site of administration and the pain conditions, the effects of MMPIP are unequivocally found only in chronic pain conditions. Paradoxically, the effect of MMPIP in the VL PAG, observable only in chronic pain and not in control conditions, is just the opposite of what was observed for AMN082 in the CeA [170, 180]. Thus, the mGluR7 negative modulation may represent a suitable target for treating pain and its affective/cognitive comorbidities [141, 179].

3.4. mGluR7 Modulation of Pain in the Dorsal Striatum

The stimulation of the dorsal striatum (electrical or chemical) inhibits pain [23-25, 182]. In this regard, the stimulation of mGluR7 in the striatum, which is located on the excitatory cortical projections, should cause an inhibition of the dorsal striatal tone and consequently produce pain. In fact, the administration of AMN082 in the dorsal striatum decreased glutamate levels, facilitated pain, increased the activity of the ON cells and inhibited that of the OFF cells of the RVM in healthy rats [33]. AMN082 in the dorsal striatum inhibited the glutamate release also in neuropathic rats. However, the effect of AMN082 on mechanical allodynia and on the activity of ON and OFF neurons of the RVM in neuropathic pain conditions was just the opposite of what was found in control rats: AMN082 inhibited pain and the activity of the ON cells while increased the activity of the OFF cells in rats with the spared nerve injury (SNI) of the sciatic nerve. The specificity of mGluR7-mediated effects of AMN082 was assessed by using ADX71743, which blocked the effects of AMN082 on pain responses in both control and neuropathic rats [33]. AMN082 in the dorsal striatum modified also the activity of the neurons of the dorsal reticular nucleus, a medullary pronociceptive area that represents the point of convergence between basal ganglia and the descending pain modulatory system (Fig. **3**). AMN082 in the dorsal striatum altered the activity of dorsal reticular nucleus neurons consistently with its facilitatory/inhibitory effect on pain responses under normal or neuropathic pain conditions, respectively. Furthermore, the inactivation of the subthalamic nucleus, STN, by lidocaine abolished the effect of AMN082 on dorsal reticular nucleus neurons only in control rats, but not in SNI rats. Thus, the dual effect of mGluR7 in facilitating or inhibiting pain responses may be due to the involvement of the two different pathways of the basal ganglia, the indirect or direct pathway, in physiological or pathological conditions, respectively [33] (Fig. **3**). In this context, it could be speculated that in pathological conditions such as neuropathic pain there is possibly a rearrangement of the basal ganglia with preferential involvement of the direct pathway.

4. mGluR8

Three isoforms of mGluR8 exist: mGluR8a, mGluR8b and mGluR8c [108, 183]. mGluR8a and 8b differ in the last 16 amino acids of the C-terminus domain whereas mGluR8c contains only the N-terminal domain (and it is likely to be a secreted protein). Like the other receptors of the group III, mGluR8 is expressed presynaptically on glutamatergic, GABAergic and monoaminergic terminals [32, 172, 184-186]. The mGluR8 is widely distributed in the CNS and in particular in the thalamus, globus pallidus, nucleus accumbens, SN, dorsal striatum and STN [110] (Figs. **1** and **2**). A lower expression of mGluR8 has been found in the cerebral cortex, hippocampus (lateral perforant path/dentate gyrus pathway), cerebellum, PAG [187] and hypothalamus [186, 188]. Low levels of mGluR8 were also found in the retina [189], spinal cord [190], central terminals of primary afferents [191] and peripheral tissues [192, 193]. Compared to mGluR7, mGluR8 has a 1000-fold higher affinity for glutamate [194], which may crucially permit its activation by glutamate spillover onto neighboring synapses in conditions characterized by glutamate elevation, preventing pathological changes in neuronal excitability. Due to the lack of selective mGluR8 ligands crossing the blood-brain barrier, the first characterization of the mGluR8 role was based, as for mGluR7, on the use of knock-out mice. Although the first study on mGluR8 knock-out mice did not show any overt pathological phenotype, with the exception of an anxiolytic-like phenotype in a conditioned fear model [195], subsequent studies have either shown an anxiogenic-like

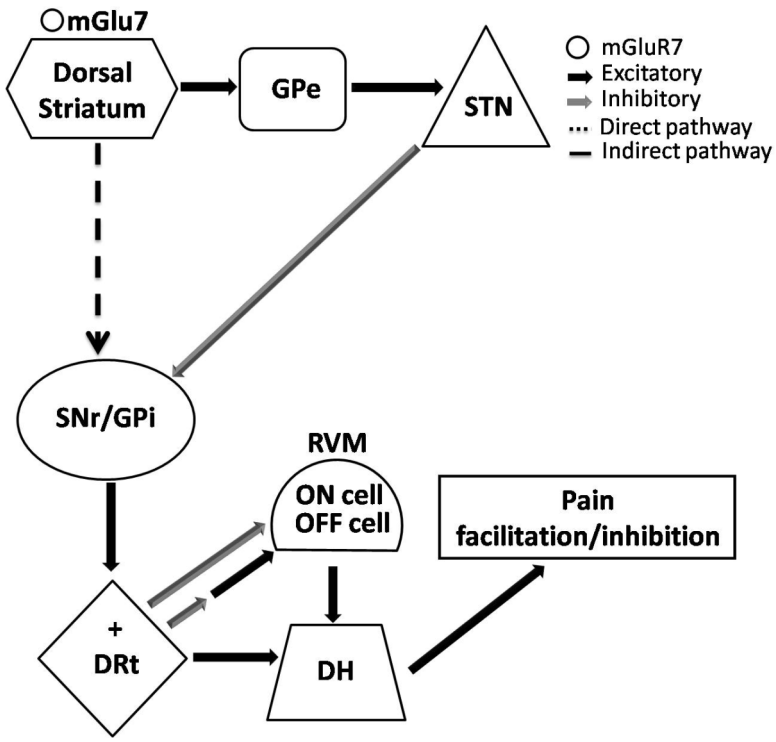

Fig. (3). Schematic representation of the connection of the basal ganglia with the descending pain modulatory system. The convergence point among the two pathways lies into the dorsal reticular nucleus (DRt), a pronocicettive area projecting in turn to the rostral ventromedial medulla and to the dorsal horn of the spinal cord. The stimulation of mGluR7 in the dorsal striatum inhibits the output projections to the direct and indirect pathway of the basal ganglia. In normal conditions the stimulation of mGluR7 reduces the activity of dorsal striatum and its inhibitory control on DRt, the dis-inhibition of which produces pain facilitation: such effect involves the indirect pathway. In pathological conditions such as neuropathic pain, the stimulation of mGluR7 reduces the activity of dorsal striatum and its inhibitory control on GPi/SNr, the dis-inhibition of which depresses the pronociceptive activity of DRt and produces antinociception. This effect involves the direct pathway. Abbreviations: SNr/GPi, substantia nigra pars reticulata and the internal globus pallidus; DRt, dorsal reticular nucleus; RVM, rostral ventromedial medulla; GPi, internal globus pallidus; STN, subthalamic nucleus; DH, dorsal horn. Excitatory and inhibitory projections are represented by grey or black arrows, respectively. The indirect paway of the basal ganglia is represented by dotted line.

phenotype [190, 196-199] or no increase in anxiety-like behavior [75, 200]. The heterogeneity of these results would seem to depend on age. In fact, mGluR8 knock-out mice displayed increased measures of anxiety starting from 6 months of age [196, 201], while no genotype-dependent difference was found in the elevated plus maze in younger knock-out mice (2 - 4 months of age), in which even more anxious-like behavior was observed in the open field [202]. Moreover, in this same test the mGluR8 knock-out mice showed either to be hypoactive [201], hyperactive [195] or have not shown any alteration of motor behavior [190, 196, 202]. It is noteworthy that mGluR4 could compensate for mGluR8 deficiency, and the lack of both receptors leads to a more anxious-like phenotype than that in which only mGluR4 or mGluR8 receptor is missing [202]. The deletion of mGluR8 increased also body weight [75, 122, 201] and impaired cognition [198, 200], this last effect was more pronounced in female than male mice [199]. In another study in which wild type and mGluR8 knock-out mice were exposed to a 2-week treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP, a parkinsonism-inducing neurotoxin, the mGluR8 knock-out mice did not display changes in motor behavior and cognitive performance showing that the deletion of mGluR8 gene protected from dopaminergic neuron toxicity [203]. Studies using mGluR8 knock-out, as well as those using mGluR7 knock-out mice, failed to define a clear role of mGluR8, possibly since mGluR8 deficiency in prenatal, postnatal or early adulthood age might prime compensatory alterations during development [202, 204, 205]. In this regard, traditional pharmacological studies are more suitable to define a clear role for mGluR8. (S)-3,4-dicarboxyphenylglycine, DCPG, has been claimed as a selective orthosteric agonist for mGluR8 with a >100-fold selectivity over other group III mGluRs [191]. DCPG has been shown to play an anticonvulsant effect [190, 206-209], inhibit alcohol self-intake and preference [210, 211], prevent amphetamine-induced locomotor hyperactivity [190] and reduce associative memory when microinjected in the amygdala [200, 212]. The systemic administration of DCPG, or 2-[[(4-bromophenyl)methyl]thio]-N-[4-(1-methylpropyl) phenyl] acetamide, AZ12216052, a mGluR8 PAM, reduced measures of anxiety [198, 211], however, when DCPG was locally administered into the amygdala it either decreased [170] or increased anxiety-like behaviour [213]. DCPG also reversed prolonged haloperidol treatment-induced catalepsy, reserpine-induced akinesia and 6-OHDA-induced forelimb use asymmetry [214]. However, the doses used to test auto-alcohol intake and amphetamine-induced hyper-

activity have also reduced spontaneous motor activity, thus the effects of mGluR8 on addiction and schizophrenia should be interpreted with caution. Moreover, in a recent study, a selective mGluR8 antagonist, the (RS)-α-methyl-3,4-dicarboxy-phenylglycine, MDCPG, blocked only the effect of a low dose of DCPG, and not that of a high dose, on the field recordings in the medial perforant path of the hippocampus, a pathway in which there is a high density of mGluR8, suggesting the activation by DCPG of another receptor than mGluR8, which has been claimed to be mGluR2 [215].

4.1. mGluR8 and Basal Ganglia

(R,S)-3,4-dicarboxyphenylglycine, (R,S)-3,4-DCPG, a mixed mGluR8 agonist and AMPA receptor antagonist, [206], induced catalepsy by itself and strongly increased the haloperidol-induced catalepsy. However, it enhanced in the central striatum the expression of proenkephalin mRNA, whose gene expression seems to parallel lesion of dopaminergic nigrostriatal pathway, in mice treated with haloperidol [216]. The above results seem to suggest that the cataleptogenic effect of (R,S)-3,4-DCPG is related to an increase in proenkephalin mRNA expression in the striatum. However, although it is not clear whether AMPA or mGluR8 contributes to above-mentioned effects, the role of AMPA receptor appears unlike owing to: i) AMPA receptor antagonists have been shown to enhance the catalepsy induced by neuroleptics [217], ii) AMPA antagonists evoke no catalepsy per se [217] and iii) the blockade of AMPA receptors increases the expression of proenkephalin mRNA [218]. Therefore, it can be only speculated here that cataleptogenic effects of (R,S)-3,4-DCPG may be rather related to mGluR8–induced inhibition of GABA release and following striatopallidal pathway activation [219].

4.2. mGluR8 and Pain

The first evidence on mGluR8 modulating pain came from a study in which the effects of both systemic and intra-PAG administration of DCPG were investigated in inflammatory and neuropathic pain models in mice. DCPG proved to be antinociceptive when systemically or intra-PAG given before, though not after, the induction of the pain state. Interestingly, the intra-PAG administration of MSOP antagonized the effect of both, systemic and intra-PAG administration of DCPG. DCPG proved also to ameliorate mechanical allodynia and thermal hyperalgesia 3 days after neuropathic pain induction but was ineffective 7 days after. Altogether, these outcomes show that mGluR8 stimulation within the PAG inhibits the development of formalin- and carrageenan-induced pain and counteracts the earlier phase of the establishment of neuropathic pain remaining ineffective in cases where the chronic pain has fully consolidated [167]. The intra-PAG DCPG administration reduced also the thermoceptive responses to tail flick and consistently reduced the activity of the pronociceptive ON cells while increasing those of the antinociceptive OFF cells in the RVM in healthy rats [168]. Plausibly, the intra-PAG administration of DCPG causes a disinhibition of the descending pain modulatory system throughout a mGluR8-mediated decrease of GABA [220]. The mGluR8 stimulation reduced pain and pain-related affective responses also when locally administered into the CeA in a model of arthritic pain induced by the injection of kaolin/carrageenan mixture in to the knee joint [170] and inflammatory pain induced by the administration of carrageenan into the hind paw [171] while it failed to modify pain behavior in control conditions [167, 170, 172]. DCPG also increased serotonin and glutamate release, whereas it decreased GABA release in carrageenan-given rats though not in control rats. DCPG into the CeA also modified the activity of ON and OFF cells in the RVM consistently with analgesia and this effect was observed only in carrageenan-given rats. In this latter an increase in mGluR8 expression on vesicular GABA transporter (vGAT)-positive profiles was also found in the CeA, consistently with the decrease of GABA release (and plausibly glutamate increase as a consequence of it) and the effect of DCPG in carrageenan-given rats only [172]. Differently from the PAG and CeA, DCPG into the NTS facilitated cardiac nociception induced by pericardial capsaicin [177]. NTS plays a facilitatory role on nociception [221] oppositely to PAG and CeA whose activation inhibits pain responses [222-224]. Thus, the stimulation of mGluR8 on GABAergic terminals depresses GABAergic interneurons projecting to the dorsal horn of the spinal cord, which normally inhibit pain transmission at the spinal level [177]. As seen for mGluR7, also for mGluR8, the pain modulatory effect depends on the brain site where it is stimulated. However, while for mGluR7 opposite responses were observed in the various pain models, the stimulation of mGluR8 seems mostly associated with pain-inhibition in chronic pain conditions while ineffective under normal conditions.

4.3. mGluR8 and Dorsal Striatum

DCPG inhibited pain also when administered into the dorsal striatum and solely in neuropathic rats remaining without any effect in control animals. In particular, DCPG increased thermal threshold and reverted mechanical allodynia, inhibited the ongoing and tail flick-evoked activity of the ON cells while increasing that of the OFF cells in the RVM. The AZ12216052, a selective mGluR8 PAM, behaved like DCPG, although less potent in increasing tail flick latency and OFF cell activity and decreasing ON cell activity in neuropathic rats. Thus, these outcomes once more indicate that the analgesic action of dorsal striatum involves the activation of RVM [24, 33]. As observed in the CeA also in the dorsal striatum chronic pain changed the expression of mGluR8 on GABAergic terminals suggesting that the pain-induced neuroplasticity affecting mGluR8 in the dorsal striatum is necessary for mGluR8 activators to be effective. Thus, the stimulation of mGluR8 on GABAergic terminals would result in extracellular GABA decrease and consequently disinhibition of antinociceptive descending pathway and analgesia in chronic pain conditions only (where an increase of mGluR8 is observed).

CONCLUSION

After the discovery of more selective compounds for mGluR4, mGluR7 and mGluR8, in particular, positive and negative allosteric modulators, several experiments were conducted to identify the role of each receptor in pain modulation. When seeking a response on pain, it is rational to ad-

minister each selective ligand, in addition to systemically, even in the areas that control pain; among these also the dorsal striatum showed an antinociceptive action. What has emerged is a rather fascinating and complicated story that we tried to summarize here. The variability of the effects produced by the stimulation of mGluR7, which are site- and condition- dependent (healthy versus pathological), may be attributable to the limitations of the only existing selective agonist, the AMN082, which in addition to showing off-target effects *in vivo* quickly produces internalization (and behaves as antagonist). Different are the effects of the negative allosteric modulation of mGluR7 that has shown to inhibit pain and its comorbidities in chronic pain conditions. Although there is a variability of responses that depend on the site of administration also for the mGluR8, there is clear evidence that the stimulation of this receptor inhibits pain solely in chronic pain conditions. mGluR4 remains the least explored with regard to pain control, perhaps because all research has focused on its striking effect on Parkinson's symptoms however its role in inhibiting pain processing at spinal level appears well defined. Finally, in the dorsal striatum, the stimulation of mGluR7 and mGluR8 inhibits pain in neuropathic pain conditions whereas the two receptors behave differently in normal conditions: mGluR7 facilitates whereas mGluR8 does not affect pain responses. In all cases, however, mGluR7 and mGluR8 (and mGluR4), expressed in the sites of the CNS controlling pain transmission, exert pain inhibiting actions when necessary, such as in conditions of pathological pain, towards which there are not yet well-tolerated and really effective drugs.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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