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EDITORIAL

Microglial histamine H_4R in the pathophysiology of Parkinson's disease—a new actor on the stage?

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Parkinson's disease (PD), the second most-common neurodegenerative disease after Alzheimer's disease, is a devastating condition which is caused by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Kalia and Lang 2015). In addition, PD patients typically develop Lewy pathology, an accumulation of protein aggregates ("Lewy bodies") in the central nervous system (CNS) that primarily consist of misfolded α-synuclein (Kalia and Lang 2015). The clinical features of PD comprise severe motor disturbances like bradykinesia, rest tremor, or muscle rigidity as well as non-motor symptoms, e.g., cognitive decline or sleep problems (Kalia and Lang 2015). Pharmacotherapy tries to compensate for the deficit of dopaminergic signaling by inhibiting dopamine metabolism (MAO-B inhibitors), by substituting dopamine (levodopa) or by directly stimulating dopaminergic receptors with agonists (Zeuner et al. 2019). Curing the disease or at least stopping its progression, however, is a yet unachieved goal.

A very important and long-neglected factor in the pathophysiology of PD and of other neurodegenerative diseases is neuroinflammation with involvement of activated microglia (Liddelow et al. 2017). Specifically, the pro-inflammatory (in analogy to macrophage activation) "classically activated" M1 type of microglia, releasing pro-inflammatory cytokines like IL1-β and TNF-α, is of specific relevance (Moehle and West 2015). Consequently, molecules that inhibit M1 microglia activation could provide a promising approach to stop the pathophysiological processes underlying initiation and progression of PD.

Literature from the recent years suggests that the histamine H_4R might be an emerging molecular target on the way to this goal. Microglial expression of functional H_4R has been demonstrated in the murine N9 microglial cell line, in murine organotypic slice cultures, and in cortical explants (Ferreira et al. 2012) as well as in primary rat microglia cells (Dong et al. 2014). Recently, in vivo data were published, showing that H_4R mRNA is present in the striatum of wild-type mice and that the H_4R agonist VUF8430 (2-[(aminoiminomethyl)amino] ethyl carbamimidothioic acid ester) as well as histamine itself cause microglial activation (Frick et al. 2016). The effect of histamine was inhibited by the H_4R antagonist JNJ-10191584 (= VUF-6002; 1-[(5-chloro-1*H*-benzimidazol-2-yl)carbonyl]-4-methylpiperazine) (Frick et al. 2016). A first association between H_4R and PD was found in a postmortem study by Shan et al. (2012). H_4R mRNA was significantly increased in the caudate nucleus and the putamen of PD patients, and a strong inverse relationship was observed between histamine methyltransferase mRNA in the substantia nigra and PD duration (Shan et al. 2012).

Now, the same research group is involved in the publication of an in vivo study in a rat model of rotenone-induced PD, suggesting a direct link between microglial H_4R activation and the occurrence of M1-activated microglia (Zhou et al. 2019). The authors used male Sprague-Dawley rats at 4 months of age. In a stereotactic surgery, 12 μg (6 μg/μl) of rotenone ((2*R*,6a*S*,12a*S*)-1,2,6,6a,12,12a-hexahydro-2-isopropenyl-8,9-dimethoxychromeno [3,4-b]furo(2,3-h)chromen-6-one) was infused into the right SNpc to induce PD-like pathology. Control animals underwent the same procedure with administration of solvent (50% DMSO/50% PEG4000) (Zhou et al. 2019). Every animal also received a permanent fixed cannula in the left lateral ventricle. Through this cannula, one of the following agents was administered for 3 weeks and at a dose of 5 μg/day: (i) the histamine H_4R-selective antagonist JNJ7777120 (1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine); (ii) the acetylcholine esterase inhibitor donepezil hydrochloride (2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride), which also suppresses microglial activation; (iii) the highly selective histamine H_3R antagonist

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carcinine dihydrochloride (3-amino-N-[2-(1*H*-imidazol-4-yl)ethyl] propanamide dihydrochloride); or (iv) saline for the control animals. Unfortunately, several experiments lack a control group of non-rotenone-lesioned animals treated with JNJ7777120 only. This was, however, at least partially compensated by the fact that rotenone was only infused into the right SNpc, while JNJ7777120 was administered into the left lateral ventricle. Thus, in the animals receiving rotenone plus JNJ7777120, the left non-lesioned side could serve as a control for endogenous JNJ7777120 effects (Zhou et al. 2019).

Immunohistochemical analysis revealed a significant (43%) loss of dopaminergic tyrosine hydroxylase-positive neurons (TH) in the rotenone-lesioned side as compared to the "healthy" contralateral side of the SNpc. This went along with a significant reduction of dopamine in the rotenone-treated part. Intriguingly, however, the deleterious effect of rotenone on dopaminergic neurons and the concomitant loss of dopamine were significantly inhibited by i.c.v. administration of the histamine H_4R antagonist JNJ7777120. By contrast, the histamine H_3R antagonist carcinine was ineffective at preventing the rotenone-induced loss of dopaminergic neurons. The authors also demonstrate that rotenone treatment causes upregulation of histamine H_4R mRNA in the ventral mesencephalon of the animals. Thus, the rat model used by Zhou et al. (2019) reflects the findings previously obtained in postmortem studies with PD patients (Shan et al. 2012). Upregulation of histamine H_4R in the rotenone-lesioned rats was almost completely inhibited by JNJ7777120 (Zhou et al. 2019).

The question, whether H_4R is involved in neuroinflammation driven by M1-activated microglia cells was extensively investigated by the authors. They show that expression of the microglial marker "ionized calcium binding adaptor molecule 1" (Iba1) was significantly increased in the rotenone-treated part of the SNpc as compared to the non-lesioned side. This effect was eliminated by the M1-selective microglia inhibitor donepezil. Interestingly, i.c.v. administration of JNJ7777120 fully mimicked the effect of donepezil (Zhou et al. 2019). The important role of the histamine H_4R in modulating M1 microglia activation in the rotenone-induced PD model was also directly demonstrated in qPCR studies. Zhou et al. (2019) show that transcripts typical of M1 microglial activation (CD86, IL-1β, or TNF-α) were significantly upregulated by rotenone, which was prevented by JNJ777120. The results for IL-1β and TNF-α were confirmed by Western blots. By contrast, transcripts typical of M2 microglial activation, Arginase1 (Arg1) and insulin-like growth factor 1 (IGF-1), were not affected by rotenone alone or in combination with JNJ7777120. Only the mRNA of the M2 marker CD206 was slightly upregulated by rotenone (non-significant trend) and even stronger by rotenone plus JNJ7777120 ($p < 0.05$) in comparison to solvent/vehicle-treated animals.

The animal model used by Zhou et al. (2019) mimics PD even with regard to α-synuclein accumulation, formation of Lewy bodies, and occurrence of motor deficits. The beneficial action of H_4R antagonism was also demonstrated with regard to these features of PD. Immunohistochemistry showed that α-synuclein aggregates were significantly reduced, when rotenone-lesioned animals had received JNJ7777120. Moreover, apomorphine-induced rotational behavior in the rotenone-treated rats was significantly ameliorated by JNJ777120 treatment.

It is well known that histamine H_4R is present on peripheral immune cells of hematopoietic origin like eosinophils (O'Reilly et al. 2002; Buckland et al. 2003; Reher et al. 2012), mast cells (Hofstra et al. 2003; Ebenezer et al. 2017), dendritic cells (Gutzmer et al. 2005; Damaj et al. 2007; Hartwig et al. 2015), or natural killer cells (Damaj et al. 2007). Zhou et al. (2019), however, administered JNJ7777120 directly into the lateral ventricle, excluding peripheral pharmacological effects of the H_4R antagonist. This is specifically important, as H_4R expression in the central nervous system had been controversially discussed during the recent years (Schneider et al. 2015; Schneider and Seifert 2016).

Microglia can be considered resident macrophages of the CNS. However, unlike peripheral macrophages, they are not hematopoietic cells, but originate from cells that migrated into the CNS from the yolk sac very early in embryonic development (Katsumoto et al. 2014). Thus, microglia represent an independent population of macrophage-like cells that does not require replenishment by peripheral monocytes. Therefore, it would be very interesting to compare peripheral macrophages and microglia cells with regard to histamine H_4R expression and function. Inconsistent data have been published regarding H_4R expression on monocytes, the precursors of peripheral macrophages (Damaj et al. 2007; Gschwandtner et al. 2013; Werner et al. 2014; Mommert et al. 2018b). With regard to macrophages, upregulation of histamine H_4R after IL-4- or IL-13-induced alternative (M2) activation was reported (Capelo et al. 2016). Moreover, a role of histamine H_4R in both M1- (Mommert et al. 2018b) and M2-activated (Mommert et al. 2018a) macrophages has been demonstrated. This is consistent with the results published by Zhou et al. (2019), where H_4R expression was enhanced in the context of microglia activation and the H_4R antagonist JNJ7777120 modulated the ratio between "neurodestructive" M1 and neuroprotective M2-activated microglia.

Zhou et al. (2019) only quantified H_4R upregulation on mRNA level in the ventral mesencephalon of the animals, but did not investigate the exact localization of the receptor. Although it is rather unlikely that the effects of JNJ7777120 observed by Zhou et al. (2019) were caused by binding to H_4R on other non-microglial cells, future experiments should aim at directly detecting H_4R expression and

function on M1- and M2-activated microglia. A direct effect of JNJ7777120 on dopaminergic neurons was excluded by the authors in cell culture experiments with rotenone-treated SH-SY5Y cells, a human neuroblastoma cell line with dopaminergic features. Rotenone reduced cell viability and caused α-synuclein upregulation, but JNJ777120 did not protect the cells (Zhou et al. 2019). It should be noted, however, that the lack of effect of JNJ777120 in SH-SY5Y cells does not necessarily exclude a direct effect on dopaminergic neurons in the animal model. First, the cells were cancer cells with probably altered properties. Second, they were from another species (human) and may show different behavior as compared to rat cells, and finally, no histamine was used to stimulate the H_4R. Thus, the results from the cell culture model should be interpreted with caution.

There are several open questions which should be investigated in future projects. First, only male rats were used by Zhou et al. (2019), because PD is about 1.5-fold more prevalent in males than in females (Moisan et al. 2016). However, recently published research suggests sex-specific differences in the development of non-motor PD symptoms (Liu et al. 2015; Cholerton et al. 2018). Thus, male and female PD rats should be compared in future behavioral studies.

Second, it is well known that the "prototypical" H_4R antagonist JNJ7777120 used by Zhou et al. (2019) is functionally selective. While JNJ7777120 is an H_4R antagonist with regard to the "classical" $G\alpha_i$-activation pathway, it acts as an agonist, when β-arrestin recruitment and MAP kinase signaling are determined (Rosethorne and Charlton 2011; Seifert et al. 2011). It remains therefore unclear whether the results observed by Zhou et al. (2019) are caused by inhibition of H_4R-mediated $G\alpha_i$-mediated signal transduction or by activation of β-arrestin signaling. Future studies should compare H_4R antagonists with different functional selectivities in animal PD models. The $G\alpha_i$/β-arrestin preferences of several classes of H_4R antagonists have been characterized in the past (Nijmeijer et al. 2012, 2013), which might serve as an orientation for future experiments.

Third, it is unclear, whether the rotenone-induced rat model of PD fully reflects all pathophysiological aspects of human PD. Rotenone, which is also used as an insecticide, causes dopaminergic cell death by inhibiting the mitochondrial complex I (Ghatak et al. 2018). The same mechanism of action is used in PD models obtained by administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or the herbicide paraquat (*N*, *N*′-dimethyl-4,4′-bipyridinium dichloride) (Ghatak et al. 2018). Alternatively, destruction of dopaminergic neurons and PD-like symptoms can be achieved by administration of 6-hydroxydopamine. Gene-based models make use of mutations in genes associated with human PD, e.g., α-synuclein, leucine-rich repeat kinase, or parkin (Ghatak et al. 2018). Thus, future studies should investigate the effect of H_4R ligands on various animal models of PD, addressing different aspects of this devastating disease. Interestingly, it has been shown in the past that endogenous histamine worsens the 6-hydroxydopamine-induced damage to dopaminergic neurons of the SNpc, presumably via the H_1R (Liu et al. 2007). Thus, other types of PD animal models seem to confirm a role of endogenous histamine in PD pathophysiology.

In the recent years, the histamine H_4R has proven to contribute to the pathophysiology of inflammatory diseases in animal models (Neumann et al. 2014) like itch (Bell et al. 2004), experimental asthma (Hartwig et al. 2015), or experimental autoimmune encephalomyelitis (Ballerini et al. 2013). Now, Zhou et al. (2019) present for the first time clear evidence for a role of the histamine H_4R in PD, a neurodegenerative disease. In addition, the results published by Zhou et al. (2019) suggest that histamine H_4R may also be highly relevant for other neurological diseases with yet elusive pathophysiology. For example, histidine decarboxylase (HDC) knockout mice, a histamine-deficient mouse model for Tourette's syndrome (Castellan Baldan et al. 2014), exhibit reduced H_4R expression (mRNA level) and an altered microglial morphology (reduced ramifications) in the striatum as well as a potentiated response of microglia to lipopolysaccharide (LPS) (Frick et al. 2016).

Another disease with still mysterious pathophysiology but a potential role of histamine is Lesch-Nyhan's disease (LND). LND, a rare disease affecting almost exclusively boys, is caused by a loss-of-function mutation in the x-chromosomally encoded hypoxanthine-guanine-phosphoribosyl transferase (HPRT) gene (Jinnah 2009). LND is associated with uric acid accumulation and juvenile gout and, most prominently, with compulsive self-injurious behavior and a loss of striatal dopamine (Lloyd et al. 1981; Jinnah 2009). The CNS symptoms are intractable and their pathophysiology remains a mystery. HPRT-deficient mice do not show self-injurious behavior, which discouraged their use as LND model (Finger et al. 1988). However, like human patients, HPRT knockout mice exhibit a reduction in striatal dopamine (Jinnah et al. 1994). Most excitingly, a reduced histaminergic neurotransmission has been shown in HPRT knockout mice (Tschirner et al. 2015), which, however, has not yet been investigated in human LND patients. It remains to be elucidated, if LND pathophysiology also involves alterations of microglial activity.

In summary, even two decades of extensive histamine H_4R research do not preclude the emergence of new surprises. Disturbances of histaminergic neurotransmission and alterations of microglial histamine H_4R function could well turn out to be the key for a better understanding of several still intractable neurological diseases with enigmatic pathophysiology.

Author contributions EHS wrote and approved the manuscript.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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