Original Research Article

Melanocortin-Driven Neuroprotection: Transcriptomic Evidence Supporting α-MSH Modulation as a Therapy in Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder marked by progressive loss of dopaminergic neurons and chronic neuroinflammation. Current treatments improve symptoms but do not halt disease progression. This study examines the anti-inflammatory and neuroprotective potential of α-melanocyte-stimulating hormone (α-MSH) in PD. Transcriptomic analysis of oxidation resistance 1 (OXR1)-activated, α-synuclein-overexpressing cells showed upregulation of melanocortin 1 receptor (MC1R) and enrichment of pathways involved in apoptosis regulation, oxidative stress response, and inflammation resolution, suggesting a shift toward cellular protection and immune modulation. Supporting murine model data further suggest that MC1R activation is associated with reduced neuroinflammation and improved neuronal survival, reinforcing melanocortin signaling as a potentially neuroprotective pathway. α-MSH and its analogs may modulate microglial activation, mitochondrial function, and redox balance, suggesting potential relevance to upstream pathological mechanisms beyond dopamine deficiency alone. These findings highlight melanocortin signaling as a promising area for further investigation in PD, though additional experimental and clinical validation is needed to determine its therapeutic applicability.

Keywords: Parkinson's disease; α-MSH; MC1R; neuroinflammation; neuroprotection; transcriptomic analysis; mitochondrial function

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder and occurs in over 10 million individuals worldwide, underscoring its substantial global health burden. It progressively declines motor function through the selective loss of dopaminergic neurons in the substantia nigra pars compacta, a region in the midbrain, resulting in a deficiency of dopamine, which is crucial for regulating movement. It manifests as bradykinesia, rigidity, resting tremors, and postural instability, hindering the performance of daily activities, independence, and overall quality of life, as shown in Figure 1. In addition to motor impairment, non-motor symptoms, including dementia, sleep disorders, and mood disorders also contribute significantly to morbidity and are accountable for increased mortality risk (1).

A population-based cohort study observed that 47.9% of PD patients had 10-year mortality, while age- and sex-matched controls had 20.3% mortality, highlighting the disease's profound impact on survival. The leading cause of death in PD patients is nervous system diseases at 38.7%, followed by circulatory diseases (15.3%), respiratory diseases (12.6%), and neoplasms (9.7%), reflecting the widespread systemic consequences of disease progression (2). The etiology of PD is complex,

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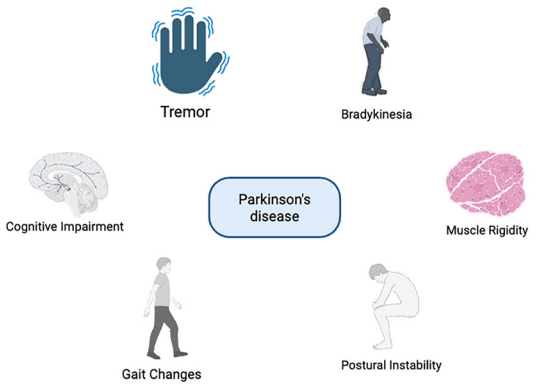

Figure 1. Key motor and non-motor symptoms of Parkinson's disease. *This figure summarizes the major clinical features of Parkinson's disease, including motor symptoms such as bradykinesia (slowness of movement), muscle rigidity, postural instability, gait disturbances (e.g., shuffling gait and reduced arm swing), and resting tremor, as well as non-motor symptoms including cognitive impairment, executive dysfunction, and memory deficits. These symptoms reflect progressive dopaminergic neuron loss and widespread neurodegeneration affecting both motor and cognitive systems.*

with the pathogenesis involving genetic susceptibility, exposure to environmental toxins, mitochondrial injury, oxidative stress, and chronic neuroinflammation, indicating that multiple interacting factors contribute to disease onset and progression. Post-mortem examination of PD brains reveals activated microglia and elevated pro-inflammatory cytokines, suggesting that sustained inflammation plays a central role in neuronal damage. Depositions of aggregated, misfolded α-synuclein are found in Lewy bodies that further compromise cellular homeostasis, disable mitochondrial function, increase oxidative stress, and trigger apoptotic processes, ultimately promoting dopaminergic neuron degeneration and reinforcing the progressive nature of the disease.

Current therapies are primarily symptom relief-oriented by restoring dopaminergic signaling with medications such as levodopa or dopamine agonists (3). Such therapies do not address underlying inflammation, oxidative stress, and neurodegeneration and decline over time. Hence, there is an urgent need for novel therapies aiming directly at disease mechanisms.

Of the most promising candidates, one is α-melanocyte-stimulating hormone (α-MSH), an endogenous neuropeptide secreted from proopiomelanocortin (POMC). α-MSH is a highly effective anti-inflammatory and neuroprotective agent that exerts its effects through the activation of melanocortin 1 receptor (MC1R), a G-protein-coupled receptor expressed on neurons, microglia, and other immune cells. Activation of MC1R blocks the release of proinflammatory cytokines, NF-κB activation, oxidative stress, apoptosis, and mitochondrial dysfunction, which are key pathological processes that drive neuroinflammation, cellular damage, and dopaminergic neuron loss in PD (4). By suppressing these interconnected pathways, MC1R signaling helps restore cellular homeostasis and protect neuronal integrity. Preclinical studies indicate that α-MSH and analogs reduce ROS, inhibit microglial activation, preserve mitochondrial integrity, and promote neuronal survival, supporting its potential as a disease-modifying therapy for PD.

Since conventional therapies cannot decelerate disease progression, interference with the α-MSH–MC1R axis is a promising therapeutic approach to reverse inflammation-mediated neurodegeneration. This work integrates narrative literature review and transcriptomic investigation of α-synuclein models of aggregation to assess the therapeutic index of α-MSH in reducing neuronal loss and maintaining cellular homeostasis in PD.

METHODS AND MATERIALS

Literature Search Strategy

A narrative literature review was conducted using the PubMed database to identify studies examining the role of α-MSH and melanocortin signaling in neurodegenerative disease. PubMed was selected because it provides access to peer-reviewed biomedical literature relevant to neuroinflammation and neuroprotection. Search terms included "α-MSH," "melanocortin," "neuroprotective," "anti-inflammatory," "Parkinson's disease," and "neurodegeneration." Inclusion criteria consisted of peer-reviewed experimental and review articles directly investigating α-MSH or melanocortin signaling in the context of neuroinflammation, oxidative stress, neuronal survival, or neurodegenerative disease. Both *in vitro* and *in vivo* studies were included to provide broader biological context, while studies lacking direct relevance to melanocortin signaling or neurodegeneration were excluded.

Dataset Selection

This study used a secondary transcriptomic analysis design based on publicly available RNA-seq data

obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database. The selected dataset, GSE295558, was derived from a large-scale bidirectional genetic screening study identifying oxidation resistance 1 (OXR1) and EMC4 as modifiers of α-synuclein aggregation (5). It was selected because it models α-synuclein aggregation, a major pathological feature of Parkinson's disease, and includes OXR1-activated conditions relevant to oxidative stress regulation and neuroprotective signaling pathways. The dataset contains gene expression profiles from HEK293 cells engineered to express human α-synuclein.

HEK293 cells are a human immortalized cell line derived from embryonic kidney tissue and are widely used in biomedical research due to their ease of culture, high transfection efficiency, and stable growth characteristics, making them suitable for genetic manipulation and disease-related pathway studies. In this experimental system, a stable HEK293 cell line was engineered to overexpress human wild-type α-synuclein (α-Syn) using CRISPR-Cas9–mediated transfection, a genome-editing technique that enables targeted gene insertion. The overexpressed α-Syn was further modified to include phosphorylation at serine 129 (pS129), a post-translational modification strongly associated with Parkinson's disease pathology. The cells were then exposed to preformed α-synuclein fibrils to induce aggregation and model disease-like conditions. Within this experimental framework, OXR1 activation was applied to evaluate its role in modulating oxidative stress responses and neuroprotective signaling pathways. In parallel, iPSC-derived neurons were used in the original study to validate whether OXR1-mediated effects observed in HEK293 cells are also present in a more physiologically relevant neuronal context, thereby strengthening the translational relevance of the findings. The experimental workflow used in this study is shown in Figure 2.

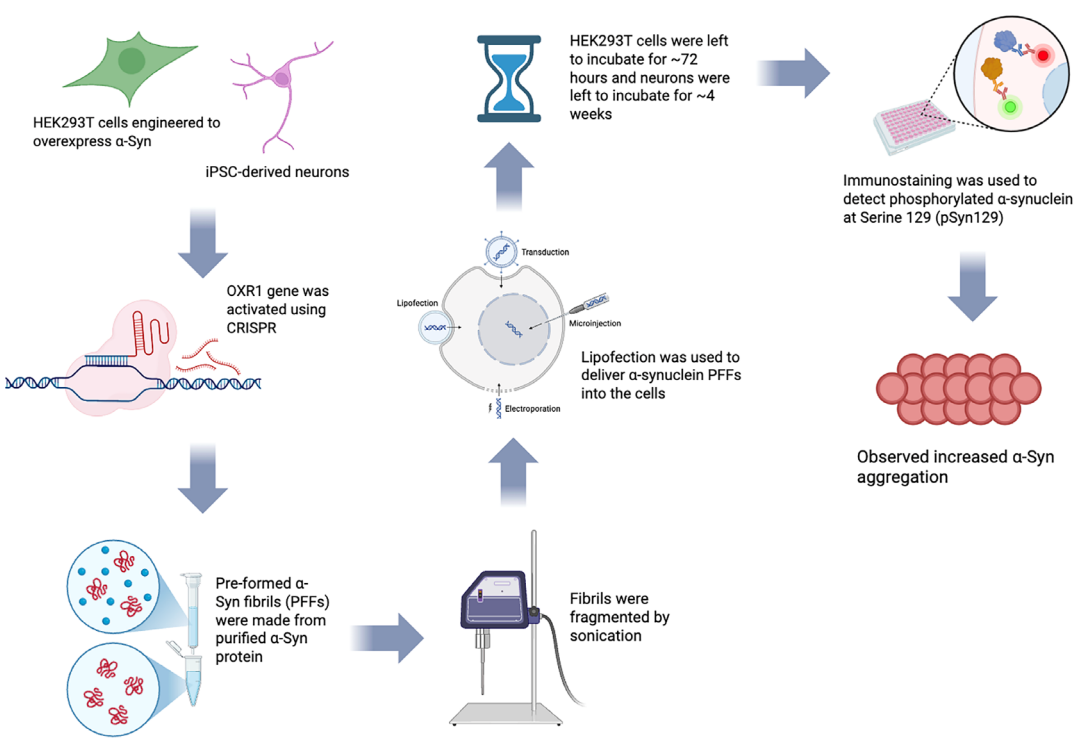

Figure 2. Experimental workflow from the source study (Reference 5) for the α-synuclein aggregation and OXR1 activation model. *This figure illustrates the experimental design used to model α-synuclein aggregation and assess the effects of OXR1 activation. HEK293T cells and iPSC-derived neurons were engineered to overexpress α-synuclein, followed by CRISPRa-mediated activation of OXR1. Pre-formed α-synuclein fibrils (PFFs), generated via sonication of purified protein, were introduced into cells using lipofection to induce aggregation. Cells were incubated for 72 hours (HEK293T) or 4 weeks (neurons), and α-synuclein aggregation was assessed using immunostaining for phosphorylated α-synuclein at Ser129 (pSyn129), indicating intracellular aggregate formation. Figure created using BioRender (www.biorender.com) based on methods described in Reference 5.*

RNA-seq Data Processing

Processed RNA-seq differential expression data were obtained from the GEO database in Microsoft Excel (.xlsx) format. The dataset included gene expression values, p-values, adjusted (corrected) p-values, and $\log_2$ fold-change values comparing OXR1-activated cells with control cells. The original dataset normalization method and differential expression pipeline (including statistical model and software) were as reported in the corresponding GEO source study. Data were sorted by ranking genes according to adjusted p-value from lowest to highest to identify the most statistically significant results. Genes with an adjusted p-value ≤ 0.05 were considered significant and retained for downstream analysis. No additional fold-change threshold was applied beyond the reported $\log_2$ fold-change values. Microsoft Excel was used for data filtering, sorting, and organization. Genes were grouped based on the direction of expression change using $\log_2$ fold-change values. Genes with higher expression in OXR1-activated cells compared to control cells were classified as upregulated in OXR1-activated cells, whereas genes with higher expression in control cells were classified as upregulated in control cells. The overall data processing and differential expression workflow is illustrated in Figure 3.

Pathway Enrichment Analysis

To examine biological processes associated with differentially expressed genes, gene lists from both groups were individually submitted to Metascape (https://metascape.org/), an online bioinformatics platform for functional annotation and pathway enrichment analysis. Gene Ontology (GO) term enrichment and pathway analyses were performed using default Metascape settings, with multiple-testing correction implemented within the platform as part of its standard analysis pipeline. Metascape outputs were used to identify the most enriched GO terms and pathways and were visualized as bar plots, bubble plots, and network diagrams generated by the software. The 100 highest-ranked GO terms for each condition were extracted and compared to identify shared and distinct biological processes. The most significantly enriched

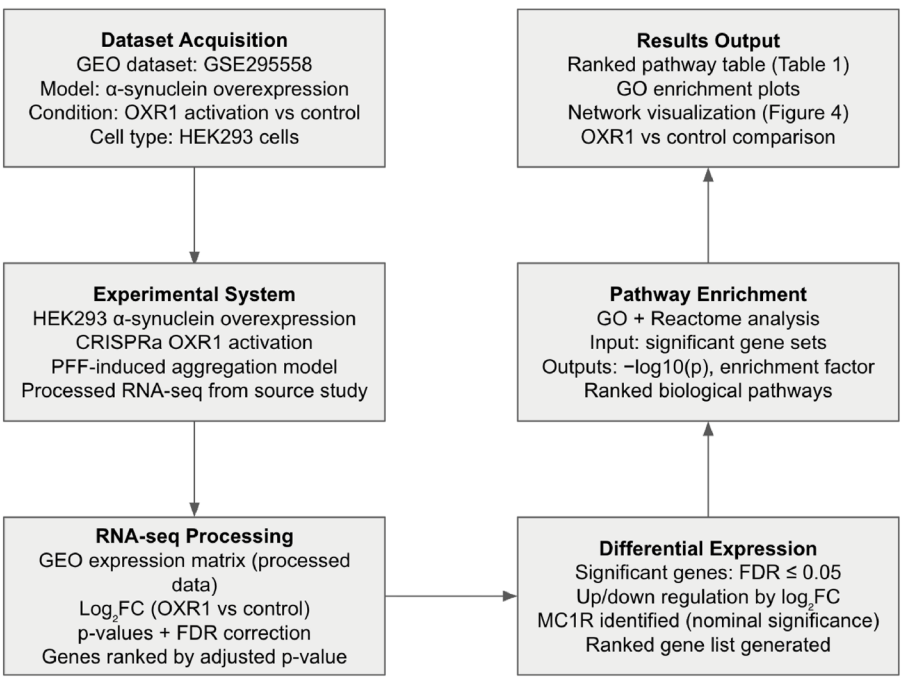

Figure 3. Overview of transcriptomic analysis workflow. *This study utilized publicly available RNA-seq dataset (GSE295558) to examine transcriptional changes associated with OXR1 activation in an α-synuclein aggregation model. Processed expression data were obtained from GEO and analyzed following the original study pipeline. Differential expression analysis using $\log_2$ fold-change and adjusted p-values identified significantly dysregulated genes, including MC1R. Significant genes were then subjected to pathway enrichment analysis using Metascape to identify key biological processes related to neuroinflammation, apoptosis, and cytokine signaling.*

biological processes, molecular functions, and cellular components were represented using ranked bar graphs, cluster networks, and enrichment heatmaps generated by Metascape.

RESULTS

Transcriptomic analysis revealed gene expression changes associated with OXR1 activation. Among the differentially expressed genes, MC1R was upregulated ($log_2FC = 0.334$; $p = 0.0073$; FDR = 0.282), suggesting a potential involvement of melanocortin signaling pathways in the OXR1-associated transcriptional response, although this change did not remain significant after multiple-testing correction and should be interpreted as a nominal association.

Beyond individual gene changes, pathway enrichment analysis identified broad alterations in biological processes related to neuroinflammation, apoptotic regulation, and cytokine signaling, as shown in Table 1. The strongest enrichment was observed in the interleukin-4 and interleukin-13 signaling pathway (Reactome: R-HSA-6785807; $-\log10(p) \approx 19.047$), indicating robust activation of anti-inflammatory immune signaling networks. Additional significantly enriched pathways included regulation of apoptotic signaling (GO:2001233; $-\log10(p) \approx 13.996$) and positive regulation of programmed cell death (GO:0043068; $-\log10(p) \approx 9.018$), suggesting that OXR1 activation is associated with coordinated modulation of cell survival and death pathways. Inflammatory response pathways (GO:0006954) were also significantly enriched ($-\log10(p) \approx 9.029$), consistent with immune-related transcriptional remodeling.

In contrast, neuron projection development (GO:0031175) showed higher enrichment in the control condition ($-\log10(p) \approx 12.361$), indicating that OXR1 activation may shift transcriptional programs away from baseline neuronal structural development toward stress-response and immune-modulatory states. Collectively, these results suggest that OXR1 activation is associated with a transcriptional profile characterized by enhanced immune signaling, altered apoptotic regulation, and differential modulation of neuronal development pathways, with MC1R upregulation providing a biologically relevant but statistically modest link to melanocortin-mediated neuroprotective signaling. These pathway enrichments are summarized in Figure 4.

DISCUSSION

The results show that OXR1 activation is associated with significant transcriptional changes in genes related to apoptosis, inflammation, and neuronal structural organization. The upregulation of MC1R in OXR1-active cells may suggest involvement of melanocortin signaling in oxidative stress and inflammation-related pathways. This is consistent with known pathological mechanisms in Parkinson's disease, where α-synuclein aggregation disrupts mitochondrial function, vesicle transport, and immune regulation, leading to a pro-oxidative, pro-apoptotic, and pro-inflammatory environment that drives dopaminergic neuron degeneration in the substantia nigra pars compacta, a midbrain region essential for dopamine production and motor control (6). OXR1, a gene encoding a mitochondrial protein involved in oxidative stress sensing and repair, regulates DNA damage responses, cell-cycle control, and apoptosis, and its activation is associated with significant changes in gene expression in this model (7). Given that both OXR1 and MC1R are involved in cellular responses to oxidative stress and inflammation, their co-regulation may reflect a

Table 1. Gene ontology and pathway enrichment analysis of OXR1-activated cells compared to control conditions. *Pathways were ranked by statistical significance based on −log10(p-value). Enrichment factor represents the degree of overrepresentation of each pathway relative to the background gene set. Gene count refers to the number of overlapping genes between the input gene list and each pathway. * Neuron projection development shows higher enrichment in control conditions compared to OXR1-activated cells.*

Rank	Pathway	Database	−log10(p)	Enrichment Factor	Gene Count
1	Interleukin-4 and Interleukin-13 signaling	Reactome	19.047	10.765	26
2	Regulation of apoptotic signaling pathway	GO Biological Process	13.996	4.324	40
3	Neuron projection development*	GO Biological Process	12.361	3.233	50
4	Inflammatory response	GO Biological Process	9.029	2.903	42
5	Positive regulation of programmed cell death	GO Biological Process	9.018	2.996	40

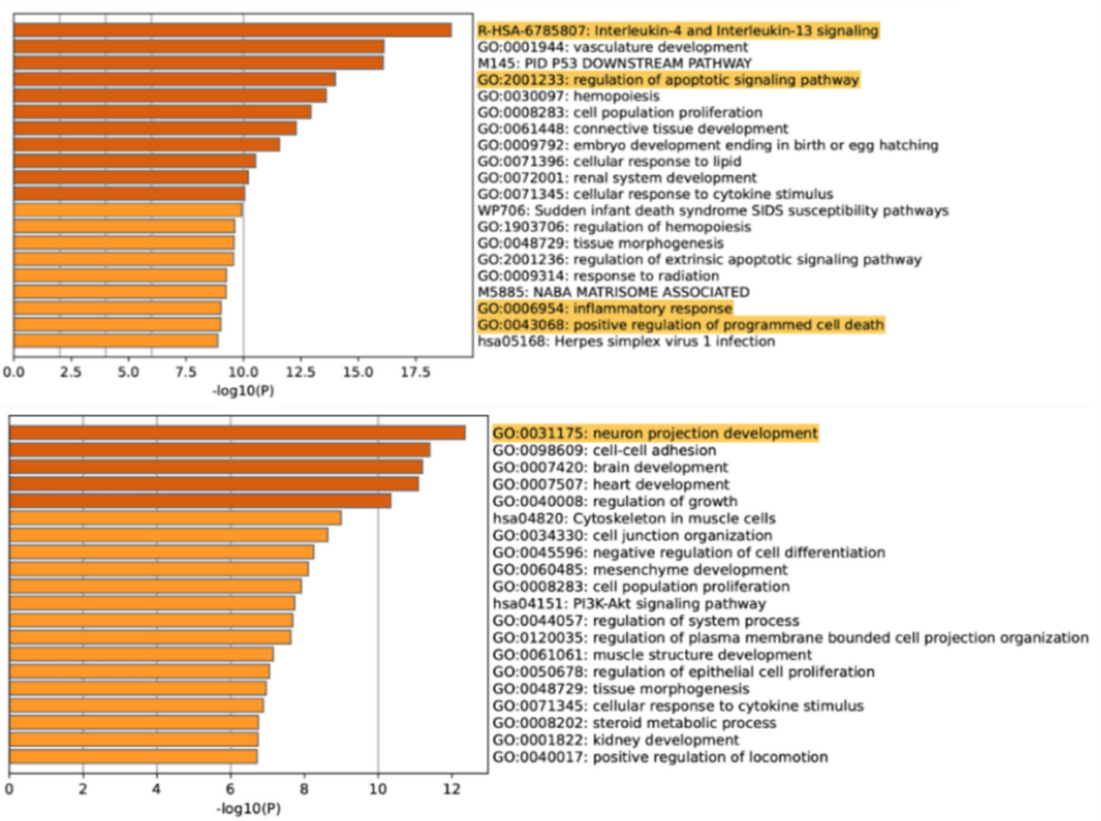

Figure 4. ***Metascape-generated Gene Ontology enrichment profile comparing OXR1-activated and control conditions.*** *This Metascape-generated figure presents the top 20 Gene Ontology (GO) biological processes ranked by −log10(p-value) from Metascape analysis, comparing OXR1-activated cells to control conditions. Key enriched pathways include inflammatory response signaling, interleukin-4 and interleukin-13 signaling, regulation of apoptotic signaling, and positive regulation of programmed cell death, while neuron projection development is more prominent in control cells. These results indicate that OXR1 activation shifts transcriptional programs toward immune modulation, apoptosis regulation, and neuroprotective signaling pathways.*

coordinated neuroprotective mechanism.

This outcome is consistent with prior work. In a separate in vivo study, mice were treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a dopaminergic neurotoxin, and lipopolysaccharide (LPS), a strong immune activator derived from bacterial cell walls (8). Mice with functional MC1R had considerably better motor function than MC1R-null mice, which suggests that MC1R contributes to neuroprotection in PD models.

The enrichment of apoptosis-related pathways such as "positive regulation of programmed cell death" and "regulation of apoptotic signaling pathway" reflects processes central to dopaminergic neuron survival. In PD, dopaminergic neuron death–particularly when excessive or unrestrained–is causative in driving disease. Dopaminergic neuron degeneration disrupts dopamine signaling (9). The neurons are especially vulnerable to oxidative stress and mitochondrial malfunction, which are the causes of abnormal protein aggregation, neuroinflammation, and neuronal death.

The functional action of α-MSH has been involved in the control of apoptosis and mitochondrial health in PD models induced by MPP+. The M17 neuroblastoma cells treated with the neurotoxin MPP+ had increased ROS, mitochondrial membrane potential disruption, ATP loss, and increased apoptotic markers. α-MSH treatment significantly attenuated these processes, preserving mitochondrial integrity, preventing oxidative stress, and restricting apoptosis in a dose-dependent manner (10).

The enrichment of the "inflammatory response pathway" (GO:0006954) aligns with established PD pathology, where microglial and astrocytic activation

drives neuroinflammation. Microglia and astrocytes, which are activated in PD, release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) that play a role in neuronal damage (11).

The strong upregulation of the "interleukin-4 and interleukin-13 signaling pathway" (Reactome: R-HSA-6785807) suggests activation of anti-inflammatory signaling programs. IL-4 and IL-13 are key anti-inflammatory cytokines that play roles in microglial polarization towards a neuroprotective phenotype, tissue repair, and inflammatory resolution. Treatments that aim to enhance IL-4 and IL-13 signaling are being considered, including cytokine-based therapies and microglial modulators (12).

Adding to this transcriptomic information, α-MSH(11-13), also known as KPV, is a tripeptide derived from the C-terminal (tail) of the larger α-MSH molecule and has been shown in studies to exhibit anti-inflammatory and neuroprotective activities in a mouse model of traumatic brain injury. These findings further present *in vivo* evidence that melanocortin-based therapies have the potential to inhibit inflammation and neuronal loss and are thus promising therapeutic leads for neurodegenerative disorders like PD (13). The higher enrichment of neuron projection development (GO:0031175) in the control group indicates baseline structural growth processes such as axon and dendrite formation (14).

Overall, the convergence of transcriptomic findings and *in vivo* models suggests that MC1R may be a potential target of interest in PD. Given that MC1R is induced by activation of OXR1 and has anti-inflammatory and neuroprotective actions, its endogenous ligand, α-MSH, or analogs may represent candidates for further investigation, as shown in Figure 5.

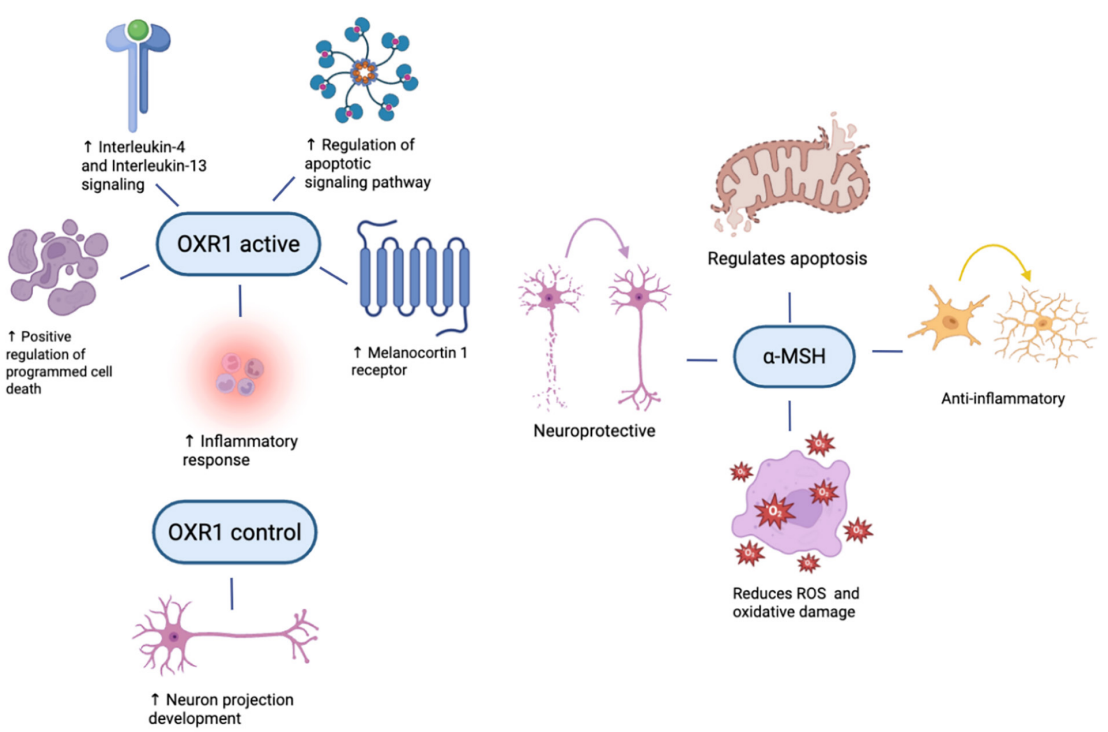

***Figure 5.* Integrated model of OXR1-driven transcriptional changes and α-MSH signaling pathways.** *This figure compares pathway-level gene expression changes between OXR1-activated and control conditions and integrates these findings with known α-MSH signaling mechanisms. OXR1 activation is associated with increased MC1R expression, enhanced IL-4 and IL-13 signaling, and upregulation of inflammatory regulation and apoptotic pathway control, whereas control conditions show higher expression of genes related to neuron projection development. These transcriptional changes mirror known α-MSH effects, including anti-inflammatory activity, mitochondrial protection, and oxidative stress reduction, supporting the proposed neuroprotective role of melanocortin signaling in Parkinson's disease. Figure created using BioRender (www.biorender.com).*

α-MSH-based therapies have shown promising preclinical action, including the inhibition of oxidative stress and apoptosis, boosting mitochondrial function, inhibition of pro-inflammatory activation of microglial cells, and induction of inflammation resolution. Native α-MSH›s disadvantage of having limited potency and excessive melanogenic activity has been addressed by synthesizing synthetic analogues that are potent but have decreased melanogenic activity. For instance, KPV inhibits microglial activation and brain injury without causing pigmentation and therefore presents as a better option for systemic delivery in chronic neurodegenerative diseases. These findings support ongoing research into melanocortin-based treatments that may be able to shift brain states from pro-inflammatory to reparative, and future investigation of combinatorial treatment strategies and delivery optimization.

Limitations

This study is limited by its reliance on a single transcriptomic dataset derived from HEK293 cells, which are non-neuronal and do not fully recapitulate dopaminergic neuronal biology in PD. Nevertheless, HEK293 systems are widely used as a primary mechanistic platform due to their suitability for controlled expression of disease-relevant proteins such as α-synuclein, making them useful for identifying early transcriptional and pathway-level responses in experimental perturbation studies. However, the absence of neuronal features such as synaptic architecture, dopamine metabolism, and neuron-specific signaling may influence how α-synuclein aggregation and melanocortin-related pathways translate to in vivo disease states. Accordingly, the results should be interpreted as reflecting general cellular stress and immune-response programs rather than neuron-specific mechanisms of PD. Finally, the study relies on computational pathway enrichment without experimental validation at the protein or functional level, meaning that the associations between OXR1 activation, MC1R upregulation, and downstream pathways remain correlative. Validation in dopaminergic or iPSC-derived neuronal models will be necessary to confirm their relevance to Parkinson's disease pathology.

CONCLUSION

This study highlights the therapeutic potential of α-MSH and the melanocortin receptor system, MC1R, as potential targets for PD. Transcriptomic profiling demonstrated that activation of OXR1 was associated with upregulation of MC1R and enrichment of anti-inflammatory and neuroprotective pathways, suggesting a possible role in modulating α-synuclein aggregation-related toxicity. The mitochondrial protective and anti-inflammatory properties previously associated with α-MSH and analogs such as KPV suggest an alternative and mechanistically distinct approach to neurodegeneration compared to current symptomatic therapies such as levodopa, which primarily restores dopaminergic signaling without addressing underlying neuroinflammation, oxidative stress, or mitochondrial dysfunction. In contrast, α-MSH has been associated with modulation of upstream pathological processes including microglial activation, NF-κB–mediated inflammatory signaling, and apoptosis regulation, suggesting potential relevance to disease progression beyond dopamine deficiency alone. Due to the limitations of current PD treatments, which do not modify disease progression, melanocortin-based therapies represent a promising area for further investigation.

Future research should move toward experimental validation of these transcriptomic findings in disease-relevant neuronal systems, including measurement of MC1R and OXR1 expression at the protein level using western blotting and immunocytochemistry. Functional studies should assess whether α-MSH or KPV treatment directly reduces oxidative stress, mitochondrial dysfunction, and apoptosis in dopaminergic neuron models by quantifying ROS levels, mitochondrial membrane potential, and caspase activation. In vivo validation using established PD models (such as MPTP-induced neurodegeneration models) will be necessary to determine whether these transcriptional changes translate into measurable neuroprotective and behavioral effects. Additionally, mechanistic studies using MC1R inhibition or knockdown could clarify whether the observed neuroprotective signatures are directly dependent on melanocortin signaling. From a translational perspective, future work should also evaluate blood–brain barrier penetration, dosing strategies, and pharmacokinetics of α-MSH analogs such as KPV to assess their feasibility as therapeutic agents in neurodegenerative disease.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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