A Review of Stearoyl Coenzyme A Desaturase in Parkinson's Disease: Linking Lipid Metabolism to α-Synuclein Aggregation

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of misfolded α-synuclein (αS), forming Lewy bodies. Growing evidence suggests that lipid composition plays an important role in αS aggregation, with monounsaturated fatty acids (MUFAs) promoting its pathological accumulation. Stearoyl Coenzyme A Desaturase (SCD), which is an enzyme that is responsible for converting saturated fatty acids (SFAs) into MUFAs, is involved in neurodegeneration. Higher SCD activity alters membrane lipid composition, increasing membrane fluidity and could enhance αS binding and aggregation. On the other hand, SCD inhibition has shown neuroprotective effects in preclinical studies, hinting at a possible involvement in PD treatments. This review presents the relationship between SCD activity, lipid metabolism, and αS aggregation, gathering evidence from in vitro and in vivo studies. By analyzing the links between SCD and αS pathology, this paper aims to clarify its role in PD progression and explore the effects of targeting SCD in neurodegenerative diseases.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra and the accumulation of misfolded α-synuclein (αS), forming Lewy bodies. This αS aggregation is a hallmark of PD and is a large contributor to neuronal toxicity and cell death. While αS is a lipid-binding protein that interacts with cell membranes, its aggregation dynamics have been shown to be influenced by lipid composition (Fanning et al., 2019). Specifically, there is some evidence to suggest that αS has a higher affinity for membranes enriched in monounsaturated fatty acids (MUFAs), which may thereby enhance its pathological accumulation (Fanning et al., 2020).

Lipids are key regulators of αS structure and function, making their role in PD an area of growing interest. One important enzyme is Stearoyl Coenzyme A Desaturase (SCD), which converts saturated fatty acids (SFAs) into MUFAs, is highly expressed in the brain, and manages neuronal lipid composition. Increased SCD activity alters membrane fluidity, which may promote αS binding and aggregation, whereas SCD inhibition is a possible treatment (Nicholatos et al., 2021). However, the precise role of SCD in αS aggregation remains unclear.

This literature review explores the relationship between SCD activity, membrane lipid composition, and αS aggregation, evaluating existing evidence from in vitro and in vivo studies.

Alpha-Synuclein: Structure, Pathological Role, And Lipid Interactions

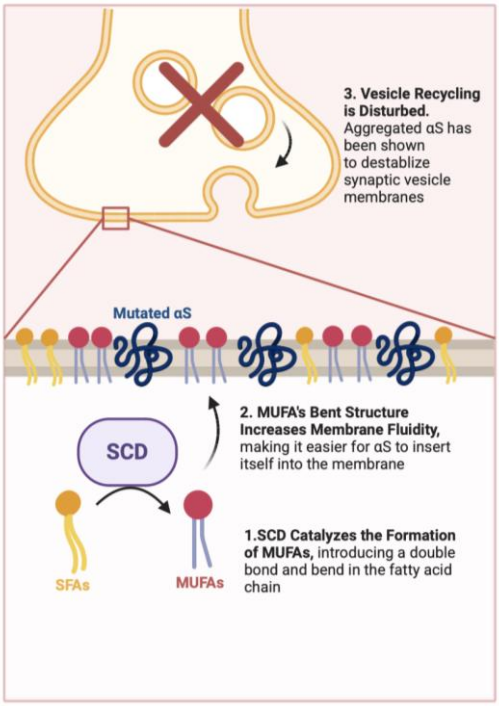
To understand the role of SCD in Parkinson's disease (PD), it is essential first to examine the function of alpha-synuclein (αS). αS is a small, neuron-specific protein that is primarily concentrated at synapses. Currently, it is hypothesized that αS helps regulate the release of neurotransmitters by interacting with synaptic vesicles- small membrane-bound sacs responsible for the storage and transport of neurotransmitters like dopamine (Calebresi et al., 2022). This process is essential for proper neurotransmission. Dysregulation of αS function, however, can cause neurodegenerative diseases like PD, where dopaminergic neurons are disproportionately affected (Farmer et al., 2020).

Under healthy conditions, αS is a soluble and functional protein. However, under pathological conditions, such as genetic mutations, oxidative stress, or mitochondrial dysfunction, αS misfolds and aggregates into insoluble fibrils. These aggregates can then form Lewy bodies, which are prominent pathological features in many neurodegenerative diseases like PD. Lewy bodies are particularly detrimental as they disrupt synaptic function and vesicle trafficking, thereby leading to neuronal damage, cell death, and neuroinflammation which can further damage neurons (Mahul-Mellier et al., 2020). Several factors contribute to αS misfolding, including genetic mutation (such as *LRRK2* and *SNCA*), which either increase αS production or enhance its susceptibility to aggregation (O'Hara et al., 2020) Post-translational modifications can also destabilize the normal structure of αS. Additionally, dysfunctions in cellular clearance mechanisms, such as autophagy and mitophagy, can lead to the accumulation of toxic αS aggregates. Dysfunctions in astrocytes and microglia-- glial cells responsible for clearing toxin proteins-- may exacerbate αS aggregation in PD. This allows αS to accumulate, damaging neurons in the process (Farmer et al., 2020).

αS is strongly linked to many neurodegenerative diseases, called synucleinopathies. Among these, PD is one of the most prominent. In PD, Lewy bodies form within dopaminergic neurons of the substantia nigra. This leads to neuron loss and symptoms like tremors, rigidity, and bradykinesia. It is thought that αS propagates from neuron to neuron, contributing to the progressive nature of synucleinopathies. Further, astrocytes and microglia may become reactive in response to αS aggregation. In their reactive state, they release cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which exacerbate inflammation and worsen neurodegeneration (Bido et al., 2021).

Importantly, αS exhibits amphipathic properties, meaning certain regions demonstrate affinities for both aqueous environments and lipid membranes. Under normal conditions, this dual interaction enables αS to maintain vesicle integrity and regulate their intracellular movement, processes that are critical for synaptic health. However, disruptions in these mechanisms contribute to the neuronal dysfunction observed in PD (Fonseca-Ornelas et al., 2021). Lipid environments within neurons are particularly important in the case of PD, as certain lipid components can influence the aggregation αS. One such lipid group is monounsaturated fatty acids (MUFAs). MUFAs, such as oleic acid, are fatty acids with one double bond in their carbon chain, and they are naturally present in cell membranes. αS preferentially associates with cell membranes enriched in MUFAs, although it does not necessarily directly cause αS aggregation (Fanning et al., 2019). Elevated MUFA levels also increase membrane fluidity and disorder (Figure 1), making it easier for αS to insert itself into cell membranes, which in turn enhances its aggregation and accumulation (Galvagnion et al. 2016).

Figure 1. *Impact of SCD on Lipid Membrane Fluidity and Alpha-Synuclein Aggregation in PD.* Figure made with the help of Biorender.com.



A 2019 study by Fanning et al. provided empirical evidence for this relationship, showing how increasing levels of oleic acid-- a major MUFA-- increase αS 3k aggregation and its neurodegenerative consequences. The researchers measured this aggregation using markers such as ATP levels, neuronal survival rates, and astrocyte reactivity; reductions in ATP and neuronal viability, alongside increased astrocyte activation, indicated heightened αS-related neuronal dysfunction and degeneration linked to elevated MUFA levels (Fanning et al., 2019). Further, increased MUFAs contribute to an environment of oxidative stress or oxidized polyunsaturated fatty acids (the main drivers of oxidative damage) that not only damages lipids and proteins, but also creates conditions that facilitate αS aggregation, forming oligomers and fibrils that contribute to neuronal dysfunction and degeneration. (Gilmozzi et al., 2020). MUFAs can also interfere with

the autophagy process, which is crucial for clearing misfolded αS, however, this could be a multifactorial outcome, and may not be directly correlated to MUFAs alone (Nicholatos et al., 2021). Thus, the relationship between αS and lipid membranes, particularly those enriched in MUFAs, is crucial for understanding the mechanisms that drive αS aggregation and neurodegenerative processes in PD.

Stearoyl-CoA Desaturase (SCD): Function and Regulation

To further explore how lipid metabolism influences αS aggregation in PD, it is important to understand the role of SCD, a key enzyme involved in the desaturation of fatty acids and responsible for catalyzing the conversion of saturated fatty acids into MUFAs. A critical function of SCD is the desaturation of palmitoyl-CoA and stearoyl-CoA to palmitoleoyl-CoA and oleoyl-CoA. This reaction utilizes oxygen (O_2) as an electron acceptor and generates water (H_2O). SCD also plays a pivotal role in energy storage and metabolic regulation (Castro et al., 2011). When these are disrupted, there may be an increased risk of obesity, diabetes, and neurodegenerative diseases.

Understanding the different forms of SCD is important for determining its role in neurodegenerative diseases. The enzyme exists in multiple isoforms that vary across species and tissue types. Rodents have four isoforms (SCD1-4) localized in distinctive tissue: SCD1 is primarily found in adipose tissue, the liver, and kidneys; SCD2 is found in the brain, as well as in adipose tissue, kidneys, and lungs; SCD3 is primarily localized to the skin; and SCD4 is largely restricted to the heart. In humans, only two isoforms, SCD1 and SCD5, have been identified. SCD1 is found throughout the body, including in adipose tissue, the liver, the brain, the lungs, and breast tissue, while SCD5 is primarily found in the brain (prefontal cortex and

cerebellum specifically) and pancreas, with additional, although lower, expression in the adrenal gland, kidneys, lungs and adipose tissue. SCD1 is also very influenced by dietary changes. SCD1 expression increases in response to a high-carbohydrate diet and decreases in response to high polyunsaturated fatty acid (PUFA) intake and fasting. Insulin levels, temperature changes, metal ions, and alcohol consumption can all also modulate SCD activity (Ntambi, 1992).

Among the two human isoforms, SCD5 is particularly relevant to PD as it is more expressed in the brain. While SCD1 is highly expressed in other parts of the body, SCD5 is more common in the brain, suggesting a more direct role in neurodegenerative processes (Sinner et al., 2012). While both isoforms contribute to metabolic and neurophysical functions, their distinct expression patterns suggest differential pathological implications. SCD1 is broadly involved in lipid metabolism, particularly in adipose tissue and the liver, whereas SCD5 appears to have a more specialized function in neuronal regulation and brain development. Importantly, SCD5 levels are also heightened in Alzheimer's Disease, implying an even stronger link to neurodegeneration (Astarita et al., 2011).

Recent studies indicate that inhibition of SCD reduces aS toxicity by shifting the ratio of the amount of MUFAs, such as oleic acid, and SFAs. Two promising SCD inhibitors, YTX-7739 and a newly specialized drug, 5b, have demonstrated efficacy in reducing lipid dysregulation associated with PD pathology (Nicholatos et al., 2021). These findings suggest that targeting SCD inhibition may represent a novel disease-modifying strategy for PD treatment.

SCD and Alpha-Synuclein: Potential Interactions

One of the primary reasons SCD inhibition emerged as a therapeutic target in PD is its prominent role in the regulation of MUFAs. SCD regulates MUFA production, and, as previously discussed, several studies have demonstrated that MUFAs promote αS aggregation. Empirical evidence directly linking SCD to PD was demonstrated by Nuber et al., who showed that the inhibition of SCD1 and SCD5 in a neuroblastoma model reduced aS aggregation, which suggests a broader role for SCD in synucleinopathies. Furthermore, inhibition of SCD prevented aS toxicity in both late-stage neural cultures (day in vitro 18+) and the 3k mutation model, a more toxic and harmful model. Interestingly, early-stage cultures appeared more vulnerable to SCD-inhibitor-induced toxicity, indicating that SCD inhibition plays a protective role in mature neurons but may potentially play a harmful one in immature neurons, specifically in the context of αS pathology. In human neural cells, SCD inhibition reduced aS formation caused by oleic acid, reduced serine-129 aS phosphorylation (a marker associated with pathological aggregation), and could potentially normalize the tetramer-to-monomer ratio of αS, which is crucial for maintaining its functional state (Nuber et al., 2021). This evidence collectively underscores the involvement of SCD in synucleinopathies.

Multiple In Vivo studies have shown that SCD inhibition can reduce αS aggregation and its associated cellular dysfunction, supporting its potential as a therapeutic target in PD. There are four key points of evidence to support this: (1) SCD inhibition reduces αS aggregation and the resulting synaptic and mitochondrial dysfunction, (2) SCD inhibition improves motor function in specific 3K αS models, (3) SCD inhibition protects dopaminergic neurons from αS-induced oxidative stress and impaired protein clearance in rat models, (4) and SCD knockout provides neuroprotection in the C. elegans model by mitigating αS misfolding and accumulation

(Nicholatos et al., 2021). In primary rat neurons, SCD inhibition was found to alleviate αS 3k-induced cellular stress in mature (late-stage) neurons. It also improved motor deficits that were associated with PD pathology (Nuber et al., 2021). These findings are consistent with the in vitro results, further validating the therapeutic potential of SCD inhibition. Additionally, SCD inhibition effectively rescued dopaminergic neurons from αS-induced degeneration in rat models (Farmer et al., 2020).

Implications for Neurodegenerative Diseases

By reducing MUFA levels, SCD inhibitors show significant potential to decrease αS aggregation and possibly slow or halt the progression of PD. One of the most extensively studied SCD inhibitors to date is YTX-7739, which is currently being assessed for its efficacy in both PD and neuroblastoma models. In one preclinical study, YTX-7739 decreased C16 fatty acid desaturation index (FADI) by approximately 80% in both cell cultures and in vivo mouse models with PD (Nuber et al., 2022). FADI, a key metric for evaluating SCD activity, reflects the ratio between saturated and monounsaturated fatty acids; thus, a reduction of this magnitude underscores the compound's effectiveness in inhibiting SCD activity. Extensive preclinical testing of YTX-7739 has also been conducted in Sprague Dawley rats and cynomolgus monkeys, with oral doses ranging from 10-90 mg/kg administered over 15 days. This treatment was well tolerated with only mild weight reduction observed (Tardiff et al., 2022). YTX-7739 is currently in Phase 1 of its clinical trials, where it was first tested in a single-ascending dose study involving 72 volunteers, who received doses ranging from 5 to 400 mg. A subsequent multiple-ascending dose study involved 16 volunteers given either 15 or 25 mg for 14-28 days. In both trials, YTX-7739 was well tolerated, with mild side effects including headaches, fatigue, and stomach pain. In Phase

1b trials, YTX-7739 was given to PD patients at a dose of 20 mg per day for 28 days. Results showed that the FADI decreased by 20-40%. Additionally, quantitative electroencephalography (qEEG) data indicated synaptic improvements in 8 out of 20 patients (Tardiff et al., 2022). Despite these promising results, however, the U.S Food and Drug Administration (FDA) halted further trials in January 2022 for safety reasons however, the specific details have remained undisclosed.

5b is also a promising SCD inhibitor. Its effectiveness was first tested in mice without PD to ensure it was able to cross the blood-brain-barrier. After this, mice were split into two groups: a control group of wild-type mice, mice with Parkinson symptoms, and 3k transgenic mice, mice with a more severe form of PD. 5b's effectiveness was evaluated by testing motor skills, monitoring αS clumping, and measuring the MUFA-to-saturated fatty acid (SFA) ratio. The results demonstrated that 5b-treated mice showed fewer tremors, improved balance, and improved walking in both WT and 3k mice compared to the placebo controls. 5b also lowered harmful deposits of αS and restored the physiological αS tetramer-to-monomer ratio. Further, the treated mice had higher amounts of dopamine, suggesting a slowing of disease progression. Notably, these benefits were observed even in mice with lower αS levels, which shows that the drug's effectiveness was due to SCD and not another factor (Nuber et al., 2020). Both YTX-7739 and 5b are shown to be promising inhibitors of SCD that could slow PD disease progression.

Future Directions and Open Questions

While the link between αS and SCD is growing, many gaps in knowledge remain. First, while MUFAs have been shown to promote αS aggregation, it is unclear exactly how and why this happens. The exact molecular interactions remain unknown. Further, there is limited information on which MUFAs specifically promote αS aggregation. Also, SCD inhibition has been shown to

harm early neuron cultures but protect late-stage neurons; what specific features develop in the neuron that make this occur is still unknown. While SCD has been shown to protect dopaminergic neurons, the underlying mechanism is not fully understood yet. Specifically, how does SCD influence dopaminergic neurons differently from other types of neurons? It is also unclear how well the animal models used in many studies reflect upon human sensitivity and susceptibility to SCD. Furthermore, SCD's long-term safety and effects on lipid metabolism are not known. While SCD could be a viable treatment option for dementia with Lewy bodies (DLB), its effectiveness on PD remains uncertain. There may be some unknown differences between SCD expression in DLB and PD, necessitating different treatment methods for the same enzyme. There are still many questions to be answered about the link between SCD and αS, though it is hoped that future research will soon address them.

Another specific challenge for the future is to find an SCD5-specific treatment, as that is what would be more effective in stopping PD progression. As of now, there have been no treatments that can target SCD5 and not SCD1, meaning both are being inhibited due to treatment (Nicholatos et al., 2021). Further, translating more potential SCD inhibitors into clinical practice requires a deeper understanding of how individuals may respond. Testing to see whether SCD inhibitors are better at slowing different kinds of PD is an important aspect that can aid in finding potential use cases for inhibitors. More clinical trials are also required to test the safety and efficacy of SCD inhibitors in people.

Another way to improve the results of SCD inhibition is to use combination therapies, where SCD inhibitors are used in addition to another treatment option. Given the multifactorial nature of PD, they could offer a better strategy for managing αS toxicity. This has a chance of improving the effects of both treatment options. Checking how effective SCD inhibition is in

addition to other treatments could help decide treatment methods for PD patients, though tests are still required to check the overall safety of this.

Given the critical role of lipid metabolism in brain function, the long-term use of SCD may raise questions about whether it would harm more than help (Farmer et al., 2020). Continued inhibition of SCD may have unwanted consequences on membranes, synapses, or myelination, which all need to be checked in preclinical and clinical trials. More long-term studies are required to discuss the effects of SCD inhibition on cognitive function, neuron integrity, and brain health.

Conclusion

The link between SCD and αS is an ever-growing one, with new studies coming out constantly. SCD influences αS toxicity by altering the ratio of MUFA and SFA balances, affecting membranes and protein clearances. Due to its complicated link with αS, SCD inhibition has been shown to reduce αS-induced neurotoxicity in cellular, animal, and primary neuron models. One potential downside to SCD inhibition is that immature neurons (DIV7) may be vulnerable to SCD inhibition, while mature neurons benefit from it. Despite this, SCD has proven to be a promising therapeutic target for PD and other synucleinopathies. To use this new treatment method, drug development is still required but only for SCD inhibitors that are brain-permeable and safe for long-term use. SCD still has many unknowns, such as the exact molecular mechanisms in which SCD inhibition reduces αS aggregation and the long-term effects of SCD inhibition on neuronal survival and function. More in vivo studies and clinical trials are required to bridge these gaps in knowledge. Going forward, it is important to explore whether SCD is beneficial for all PD patients or only specific individuals, as it may help to understand where and when it can be used.

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