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NEUROPROTECTIVE EFFECT OF RESVERATROL IN A ROTENONE-INDUCED RAT MODEL OF PARKINSON'S DISEASE

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Abstract

Parkinson's disease has no disease-modifying treatment, and the pesticide rotenone is widely used to reproduce its mitochondrial and oxidative features in rodents. Resveratrol, a plant polyphenol with antioxidant and sirtuin-related activity, has been studied as a neuroprotective candidate in this and related models. This review summarises published work on the rotenone rat model, the pharmacology of resveratrol, and evidence for protection in toxin-based parkinsonism, and it reports no new experimental data. Studies describe preserved dopaminergic neurons, reduced oxidative stress and better motor performance, but doses vary, the model is inconsistent, and resveratrol has poor bioavailability. Translation to patients is unproven, and standardised, well-reported preclinical studies are needed.

1. INTRODUCTION

Parkinson's disease is the second most common neurodegenerative disorder, and its prevalence is rising as populations age. Patients develop tremor, rigidity and slowness of movement as dopamine-producing neurons in the substantia nigra pars compacta die, and Lewy bodies rich in aggregated alpha-synuclein appear in the survivors [1, 2]. Levodopa and other dopaminergic drugs relieve the motor symptoms for years, but they do not slow the underlying neuronal loss, and long-term therapy brings motor fluctuations and dyskinesias. A treatment that protected neurons would change the picture,

which is why neuroprotection remains one of the field's main aims and one of its most frequent disappointments. Epidemiological work has also tied environmental exposures such as pesticides to risk, which is one reason why toxin-induced animal models have attracted so much attention [3, 4]. For a pharmacist or clinical scientist, understanding these models is a prerequisite for judging the claims made for any candidate neuroprotective agent.

Several processes are thought to drive the degeneration, including mitochondrial dysfunction, oxidative stress, protein misfolding, impaired autophagy and neuroinflammation. A deficiency of mitochondrial complex I was found in the nigra of patients several decades ago, and oxidative damage to lipids, proteins and DNA has been repeatedly documented [5, 6, 7]. These findings made antioxidants and mitochondrial protectants attractive candidates for slowing disease, and dietary polyphenols have drawn particular interest because they are cheap, widely consumed and appear safe [8]. Among them, resveratrol (3,5,4'-trihydroxystilbene), found in grape skins, berries and peanuts, has been studied most. Evidence that a compound protects neurons in a dish does not guarantee it will in a living animal, and evidence in an animal does not guarantee benefit in patients. The history of the field shows how easily preclinical optimism can run ahead of what the pharmacology and the models can support [1, 2].

Testing such agents requires animal models, and none is perfect. This review concentrates on one, the rotenone-induced rat model of Parkinson's disease, and on the evidence that resveratrol protects dopaminergic neurons and behaviour in it and in related toxin models. It reports no new experimental data. Instead, it draws on published experimental papers, reviews and methodological reports to ask what the model can and cannot show, what is known about resveratrol's pharmacology that bears on brain exposure, what protective effects have been described, and which weaknesses of design and reporting limit confidence in the results [9, 10]. The discussion is organised from model to compound to effect. The next section describes the rotenone model and its problems, the following one summarises what is known about resveratrol as a drug, and a third reviews the published protective findings before the limitations and the translational outlook are considered [7, 8].

2. THE ROTENONE MODEL

Rotenone is a natural insecticide extracted from the roots of leguminous plants, and it is a potent, lipophilic inhibitor of mitochondrial complex I. In their landmark study, Betarbet and colleagues infused rotenone intravenously into rats for several weeks and reported selective degeneration of nigrostriatal dopaminergic neurons, together with cytoplasmic inclusions containing alpha-synuclein and behavioural features of parkinsonism, which suggested that chronic systemic complex I inhibition could reproduce key aspects of the human disease [3]. The paper triggered a wave of work with the agent and made rotenone a standard tool in the field. The agent crosses membranes freely and does not need a transporter to enter cells, which helps to explain why a systemic dose can produce a lesion limited largely to the nigrostriatal system, even though complex I is present in every cell. Susceptibility of dopaminergic neurons to oxidative injury is the usual explanation [3, 11].

The appeal of the model is partly epidemiological. Case-control and cohort studies have linked pesticide exposure with higher risk of Parkinson's disease, and in a study of agricultural workers, use of rotenone or paraquat was associated with a markedly increased risk, of around two- to threefold [4]. Rotenone also reproduces features that toxin models such as 6-hydroxydopamine do not, notably the formation of alpha-synuclein-positive inclusions and effects beyond the nigra [12]. For a study of a polyphenol that acts on mitochondria and redox balance, a complex I inhibitor is a logical challenge, since the mechanism of injury and the proposed mechanism of protection overlap. Rotenone is also used as a pesticide and a fish poison, and its presence in the environment gives the model a credibility that purely synthetic neurotoxins lack. Whether the doses given to rodents resemble

real exposure is a separate question, since experimental regimens are designed to produce a lesion within weeks [4, 12].

Mechanistic work has shown that the picture is more complex than energy failure. Sherer and colleagues found that rotenone caused oxidative damage and selective toxicity to dopaminergic neurons at concentrations that did not deplete adenosine triphosphate, which implied that reactive oxygen species rather than bioenergetic collapse drove the injury [11]. Microglial activation, impaired proteasomal function and disturbed vesicular storage of dopamine have been reported as well. These multiple routes mean that a protective agent can act at several points, and that readouts such as lipid peroxidation, glutathione levels and mitochondrial enzyme activity can be informative about what the agent does. In practical terms this means that antioxidants, iron chelators and mitochondrial cofactors are among the agents most often tested in the model, and that a positive result can be read as supporting a particular pathway of injury, provided the corresponding markers are measured and not simply assumed [7, 11].

The model is also notoriously difficult. Early studies in Lewis rats gave a variable lesion, with some animals showing marked nigral loss and others none, and with a significant fraction developing systemic toxicity or dying [9]. A later group described a highly reproducible protocol using intraperitoneal injection of rotenone in a specific vehicle in Lewis rats, with a clear dopaminergic lesion and a dose-dependent effect [13]. Strain, route, vehicle, dose and duration all matter, and other strains such as Sprague-Dawley and Wistar behave differently. In mice, the effects of long-term administration were less consistent still [14]. Papers should state these parameters in detail. Welfare considerations come with the territory. Rotenone-treated animals can lose weight, become hypokinetic and show distress, and ethical review bodies expect humane endpoints, careful monitoring and justification of group sizes. Compared with the MPTP mouse model [15], the rotenone protocol has often demanded more intensive care for each animal [9, 13].

3. PHARMACOLOGY OF RESVERATROL

Resveratrol is absorbed well from the gut but reaches the circulation as the parent compound in only tiny amounts. In a human study using radiolabelled drug, at least 70 per cent of an oral dose was absorbed, yet peak free resveratrol in plasma was extremely low, because the compound is rapidly converted to glucuronide and sulfate conjugates in the intestine and liver [16]. The conjugates persist longer than the parent, and they may act as a reservoir that can be partly deconjugated in tissues. Reviews of human data conclude that bioavailability is low, that variability is large, and that doses of several grams per day are needed before the parent compound is measurable [17, 18]. Plasma concentrations after oral doses in rodents are likewise low for the parent compound, and the reported protective doses should be read alongside what is known about the species handling of the drug. Terminal half-life is short and clearance rapid, which means repeated daily dosing is needed to maintain any exposure [17, 18].

Mechanistic claims for resveratrol have changed over the years. Early reports that it activated the deacetylase SIRT1 and extended lifespan in yeast stimulated great interest [19], and in mice fed a high-fat diet, resveratrol was reported to improve mitochondrial function and protect against metabolic disease through SIRT1 and the coactivator PGC-1α [20]. Subsequent biochemical work, however, showed that the apparent direct activation of SIRT1 in the original assay depended on the fluorescent substrate used, and that resveratrol was not a direct activator of the enzyme with natural substrates [21]. Its cellular effects may be mediated indirectly, for example via AMP-activated protein kinase. The disagreement is not merely academic. If resveratrol does not act through direct SIRT1 activation, then claims that its neuroprotective effects are proof of that mechanism are weakened, and attention shifts to its antioxidant, AMPK-related and anti-inflammatory actions, each of which can be tested separately [20, 21, 22].

Other actions are better established in simple systems. Resveratrol scavenges free radicals,

modulates nuclear factor erythroid 2-related signalling and inhibits cyclooxygenases, and it appears to reduce microglial activation in several settings [8, 18]. In neuronal cell cultures, it protected against oxidative stress and against toxicity induced by alpha-synuclein, an effect that was partly dependent on SIRT1 [23]. In cellular models of Parkinson's disease, it also activated the AMPK-SIRT1 axis and promoted autophagy [22]. The caveat, as with any polyphenol, is that concentrations used in vitro are often much higher than those reachable in brain tissue after oral dosing. Put simply, laboratory studies show that resveratrol can protect cultured neurons, but the concentrations that did so were frequently in the micromolar range. Whether similar levels occur at the site of action in an animal given a modest oral dose is the question that most preclinical papers leave unanswered [16, 23].

Brain exposure is the missing link in most arguments for neuroprotection. A compound must reach the substantia nigra and striatum at concentrations that act on the proposed targets, and resveratrol faces rapid conjugation in the gut and liver that limits the parent form available to cross the blood-brain barrier. Studies in rodents have detected the parent compound and its metabolites in brain tissue after high doses, but the proportion is small, and the biological activity of the conjugates is uncertain. Formulation approaches such as nanoparticles, and structural analogues designed to resist conjugation, aim to improve this step, and they are an active line of research [16, 17, 18, 24]. Reports of tolerability in volunteers at high doses add to the picture but do not tell us about brain concentrations.

The mitochondrial biogenesis pathway has particular relevance. Overexpression and activation of PGC-1α protected dopaminergic neurons in the MPTP mouse model, indicating that increasing mitochondrial capacity can buffer a complex I insult [25]. If resveratrol influences this pathway, even indirectly, then a protective effect in a complex I toxin model would be mechanistically coherent. That reasoning is a hypothesis, and not an established fact; the link from resveratrol exposure to PGC-1α activation in brain tissue has been shown in cells and a few animal studies but remains to be confirmed in the dopaminergic system under rotenone.

4. PROTECTIVE EFFECTS IN PARKINSONIAN MODELS

Direct evidence in rotenone-treated rats is limited but suggestive. An experimental study of resveratrol formulated as nanoparticles reported that the preparation improved behavioural deficits and reduced markers of oxidative stress and mitochondrial dysfunction in rats exposed to rotenone, and it was more effective than the free compound at the same dose, which the authors attributed to better delivery [24]. Such results fit the broader finding that poor bioavailability limits resveratrol, and that formulations improving exposure may reveal effects obscured by weak delivery. Nanoparticle carriers can protect the compound from rapid conjugation and may help it cross barriers, though evidence on how much reaches the brain tissue is limited. The study is useful as a pointer, but it comes from a single laboratory and has not been independently reproduced [16, 17].

Evidence from other toxin models widens the picture. In rats lesioned with 6-hydroxydopamine, resveratrol treatment attenuated oxidative damage and the depletion of dopamine in the striatum and improved rotational behaviour in several studies [26, 27]. In mice treated with MPTP, it reduced the loss of nigral neurons and preserved striatal dopamine, and one study ascribed the effect to free radical scavenging [28, 29]. These models differ from rotenone in mechanism, but all involve oxidative injury of dopaminergic neurons, so agreement among them supports a general neuroprotective effect against oxidative stress. None of these studies used rotenone, so they cannot confirm that the effect holds against a complex I inhibitor. They do show that resveratrol is not inert in toxin models and that the neurochemical changes are broadly in the direction expected for an antioxidant [11, 24].

Mitochondrial and autophagy pathways offer a mechanistic explanation for the findings.

Activation of the transcriptional coactivator PGC-1α, which drives mitochondrial biogenesis, protected dopaminergic neurons in the MPTP model, and resveratrol has been proposed to act on the same pathway through AMPK and SIRT1 [20, 25]. In cellular models of Parkinson's disease, resveratrol activated AMPK and SIRT1 and promoted autophagic clearance, which could help to remove damaged mitochondria and misfolded proteins [22]. These links are plausible, but they have been shown mostly in cells and need confirmation in animals exposed to rotenone [23, 25].

Outcome measures have included behavioural tests, neurochemistry and histology. Motor performance has been assessed with the rotarod and open-field tests, and with the cylinder test, which measures forelimb use asymmetry in unilateral models [30, 31]. Neurochemical readouts include striatal dopamine and its metabolites, while histology relies on tyrosine hydroxylase immunostaining of nigral neurons. Oxidative stress is followed through malondialdehyde, glutathione, superoxide dismutase and catalase. The combination of tests is reasonable, but some studies report only a subset, and few use blinded assessment or stereological counts that would give robust cell numbers [9, 32]. Cell-level observations support the same picture. Resveratrol reduced toxicity from alpha-synuclein in neuroblastoma cells, and activation of AMPK and autophagy has been described in other cellular models of the disease, though these systems lack the complexity of an intact brain [22, 23]. The relative scarcity of work using rotenone itself is therefore a limitation of the evidence base, and not merely a feature of this review.

The main published findings are brought together in table 1, which sorts entries by model and type of evidence. Most entries concern oxidative and neurochemical outcomes, fewer concern behaviour, and very few concern alpha-synuclein pathology or inflammatory markers. The distribution of entries between groups is shown in fig. 1. A fair reading is that resveratrol protects dopaminergic neurons against several toxins in rodents, that the evidence in the rotenone model specifically is thin, and that direct comparisons of doses and routes are scarce [24, 26, 29]. Because the table mixes models, readers should not pool the entries into a single estimate. Differences in species, toxin dose, resveratrol formulation and follow-up make quantitative comparison inappropriate, and the table is intended as a map of evidence rather than a meta-analysis [3, 13].

5. LIMITATIONS AND TRANSLATION

Several limitations restrict how much weight these studies can bear. Group sizes are usually small, randomisation and blinding are seldom reported, and sex is often not considered. A systematic comparison of animal experiments with clinical trials found that treatment effects often failed to carry over, and that weak design and incomplete reporting, including poor description of sample size and allocation, were common in the animal literature [32]. In the rotenone model, uncertainty about lesion severity and mortality complicates the interpretation of treatment effects, since a protective drug may simply lower toxicity by changing the absorption or metabolism of rotenone. Publication bias is another worry, since a laboratory that finds a polyphenol to be inactive in a toxin model is less likely to write the result up than one that finds a benefit, so the published record may overstate efficacy [1, 32].

Pharmacokinetic mismatch is a second issue. Rodents dose heavily compared with human intake, and rat metabolism of resveratrol differs from that in humans. Whether protective concentrations reach the brain is rarely measured. Where brain levels have been assessed, parent resveratrol was a small fraction of what was given, and conjugates predominated [16, 17]. Studies that report neuroprotection at oral doses without measuring exposure leave open the possibility that the effect arises from peripheral actions, for example on gut microbiota or systemic inflammation, rather than direct action in the nigra. Rotenone also has peripheral toxicity, including effects on the gut, which is relevant because resveratrol is given orally and may interact with rotenone in the gastrointestinal tract. Where drug and toxin are both given by mouth, absorption interactions have to be

excluded before protection is attributed to a pharmacological effect [9, 17].

Table 1: Published findings on resveratrol and related evidence in parkinsonian models

Model or study	Reported finding	Ref.
Rotenone in rats Intravenous infusion	Selective nigrostriatal degeneration with alpha -synuclein-positive inclusions and parkinsonian behaviour.	[3]
Rotenone in rats Intraperitoneal protocol	Reproducible dopaminergic lesion with dose-dependent effects in Lewis rats.	[13]
Rotenone in rats Mechanism	Oxidative damage and selective neuronal toxicity occurring without ATP depletion.	[11]
Resveratrol nanoparticles Rotenone rats	Improved behaviour and oxidative markers, and greater effect than free drug.	[24]
Resveratrol 6-hydroxydopamine rats	Reduced oxidative damage and dopamine depletion in the striatum.	[26, 27]
Resveratrol MPTP mice	Preserved nigral neurons and striatal dopamine, linked to free radical scavenging.	[28, 29]
Resveratrol and SIRT1 Cell cultures	Protection against alpha-synuclein toxicity and oxidative stress, partly SIRT1 dependent.	[22, 23]
Resveratrol and SIRT1 Biochemical assays	Direct activation of SIRT1 not confirmed with natural substrates.	[21]
Resveratrol pharmacokinetics Humans	High absorption but very low bioavailability of the parent compound.	[16, 17]
Resveratrol trial Alzheimer's disease	Well tolerated, no clear clinical benefit, unexplained brain volume loss.	[33]

Species and sex are further variables that deserve mention. Most rotenone studies use young adult male rats, whereas Parkinson's disease affects both sexes and typically starts late in life. Oestrogen has been reported to influence vulnerability of dopaminergic neurons in toxin models, and age affects both mitochondrial function and drug metabolism. Studies in aged animals of both sexes would be more informative, though costlier and more demanding. Until they are done, the generality of protective effects of resveratrol across ages and sexes remains an assumption and not a finding [9, 13, 32].

Clinical evidence is scarce and not encouraging. A randomised trial of resveratrol in mild to moderate Alzheimer's disease found the compound to be well tolerated and measurable in cerebrospinal fluid, but it did not show clear benefit on biomarkers or clinical measures, and an unexplained greater loss of brain volume was seen in the treated group [33]. No comparable trial in Parkinson's disease has established benefit. The history of neuroprotective trials in the disease, in which agents with striking preclinical results failed, argues for caution in extrapolating from toxin models to patients [1, 2]. A related lesson came from the sirtuin field, where enthusiasm based on early positive results was tempered when later experiments failed to reproduce the proposed mechanism. The episode is a reminder that independent replication is an essential part of building confidence in any neuroprotective claim [19, 21]. Shared protocols would make this easier.

Alternative neuroprotective strategies offer a sobering comparison. Antioxidants such as vitamin E and coenzyme Q10 showed encouraging results in cell and animal studies, yet trials in patients failed to show slowing of disease progression. The same pattern has been seen with several other agents carried forward from toxin models. This does not mean resveratrol will fail, but it does mean that a good result in a rotenone or MPTP rat is a first step and not a prediction. Combination approaches, earlier intervention in people at risk, and better progression biomarkers are widely discussed responses to the problem [1, 2].

6. CONCLUSION

Published work suggests that resveratrol protects dopaminergic neurons against several toxins in rodents, probably through antioxidant, mitochondrial and autophagy-related actions, and the rotenone model is a logical setting in which to test it because it injures neurons through complex I inhibition [3, 11, 24]. Direct evidence in rotenone-treated rats is limited to a few studies, and most support comes from related toxin models and cell cultures.

The model's variability, small and incompletely reported experiments, poor oral bioavailability and absent clinical confirmation temper these findings [13, 16, 33]. Standardised protocols, delayed-treatment designs, measurement of brain exposure and transparent reporting would make future studies more informative. For now, resveratrol is best viewed as a mechanistically interesting candidate and not an established neuroprotective therapy.

7. ABBREVIATIONS

AMPK-AMP-activated protein kinase, ATP-Adenosine triphosphate, MPTP-1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PGC-1α-Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, 6-OHDA-6-Hydroxydopamine, SIRT1-Sirtuin 1

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9. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

10. CONFLICT OF INTERESTS

Declared none

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