Results and interpretation of a self-monitored experiment of a broccoli seed tea on the symptoms of 8 people with Parkinson's disease.

Albert F Wright

On learning that a very promising and potentially disease-modifying therapy for Parkinson's disease, based on a natural product and supported by years of outstanding research, had been abandoned rather than being tested on humans, a well-informed group of Parkinson's disease patients decided to carry out the experiment for themselves. Although most of them had no scientific training, they co-ordinated their efforts and pooled their observations. to complete an experiment using a broccoli seed tea. These "Patient-Researchers" demonstrated that by working together intelligently and sharing their personal interpretation of their own symptoms, patients in today's connected world have the ability to enhance our knowledge of disease.

Their contribution brings new insight to the decades of intellectual achievement and critical experimentation by leading researchers which led to the development of the remarkable hypothesis which implies that activating the genetic transcription factor Nrf2 with sulforaphane made from broccoli seeds can counter oxidative stress and damage to mitochondria in the neurons of people with Parkinson's disease. This hypothesis had never been subjected to its most critical test; *applying it to people with Parkinson's disease.* The very modest experiment described here, possibly the first to test that theory, carefully executed by 8 Parkinson's disease patients in their own homes, has demonstrated that non-motor symptoms can be rapidly attenuated by this tea containing sulforaphane.

Broccoli seed extract to reduce oxidative stress in Parkinson's disease
Symptom Record

Identity code: Fdd/mm/yy			**Starting date: 10/25/20**				
Symptom	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Daily product quantity (g)	0	0,5	0,5	0,5	0,5	0,6	0,6
Number of doses per week	7	7	7	7	7	7	7
Daytime urinary urgency	1	1	1	1	1	1	1
Nocturnal urinary frequency	1	1	1	1	1	1	1
Constipation	1	1	1	1	0	0	0
Mood changes	1	1	0	0	0	0	0
Brain fog	1	1	0	0	0	0	0
Lack of motivation	1	0	0	0	0	0	0
General fatigue	1	0	1	0	0	0	0
Sleep quality	1	1	1	1	1	0	0
Dreams, Rem sleep	0	0	0	0	0	0	0
Memory	1	1	1	1	1	0	0
Sense of smell	1	1	1	1	1	1	1
Total non-motor	**10**	**8**	**7**	**6**	**5**	**3**	**3**
Dyskinesia,	0	0	0	0	0	0	0
Dystonia	0	0	0	0	0	0	0
Slowness	1	1	1	1	1	1	1
Rigidity	1	1	1	1	1	1	1
Hand pain	1	1	1	1	1	1	1
Leg pain	0	0	0	0	0	0	0
Balance	1	1	1	1	1	1	1
Speech difficulty	0	0	0	0	0	0	0
Soft voice	0	0	0	0	0	0	0
Eye fatigue	0	0	0	0	0	0	0
Swallowing	0	0	0	0	0	0	0
Coordination	1	1	1	1	1	1	1
Typing ability	1	1	1	1	1	1	1
Walking	0	0	0	0	0	0	0
Tremor	1	1	1	1	1	1	1
Total motor	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Total symptom score	**17**	**15**	**14**	**13**	**12**	**10**	**10**
Overall evaluation							
Notes	a		b				
Events		1		2			

0: insignificant or absent, 1: moderate but manageable, 2: severe or difficult to manage, 3: major handicap or disabling.

Fig. 1: *Example of a completed symptom record sheet with entries reclassified into two subgroups: non-motor and motor symptoms.*

The 6 week program started with a very low dose of the tea. Participants completed a weekly chart reporting their perceived intensity of 26 symptoms of the disease (presented in random order), also commenting on any adverse effects. If a symptom was perceived to show improvement, participants were requested stay on the same dose of broccoli seed tea. Alternatively, participants could slowly increase the dose each week until a symptom improvement was observed, or up to a maximum recommended dose.

8 participants completed the program while correctly adhering to the protocol. These results concern only these 8 participants

Results

The improvement in symptoms was particularly marked for a subgroup commonly referred to as non-motor symptoms. In comparison, motor symptoms improved only very modestly over this timescale (Fig. 2). Of the 8 participants, 5 reported very strong improvements in non-motor symptoms (Fig. 3) whilst 3 participants, who started the program with very low non-motor symptoms, showed almost no improvement in any symptoms.

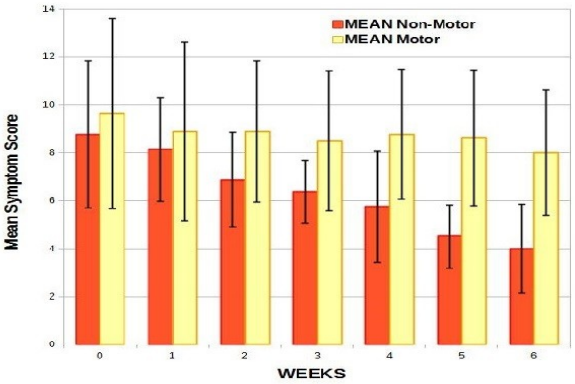

Fig. 2: *Evolution of mean symptom scores of non-motor and motor symptoms for all 8 participants. Error bars are standard deviations.*

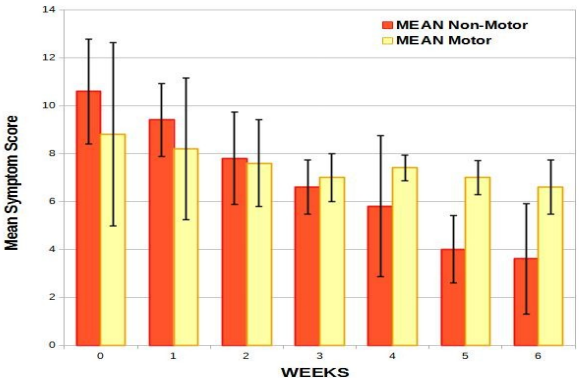

Fig. 3: *Evolution of mean symptom scores non-motor and motor symptoms for the 5 best responders. Error bars are standard deviations.*

Mean differentiated symptom scores

The results show a marked differentiation in the mean scores of non-motor symptoms compared to those of motor symptoms for all 8 participants. This is even more apparent when the 5 best responders are considered. This improvement in non-motor symptoms was observed continuously over the 6 weeks of treatment.

Individual symptom data

Summed over all 8 participants, the most prevalent symptoms at baseline were fatigue, sleep quality, lack of motivation and loss of sense of smell. Fatigue and lack of motivation were also those most attenuated over the course of the experiment, fatigue being reduced by 90%. Loss of sense of smell was unchanged.

Interpretation

Placebo effect: These results are not consistent with a typical placebo effect in Parkinson's disease. The placebo effect in Parkinson's disease is usually observed as an improvement in motor symptoms due to a positive patient expectation of reward that increases the production of dopamine.

Oxidative-stress-induced mitochondrial dysfunction leads to energy deficiency in dopaminergic neurons of Parkinson's disease patients: The impact of oxidative stress on the integrity of mitochondria in neurons is emerging as a major component of the early phase of Parkinson's disease. Oxidative stress, mitochondrial dysfunction and energy deficiency are implicated in many neurological and neurodegenerative diseases, despite them not being classified as mitochondrial diseases. Oxidative stress associated with mitochondrial dysfunction has been demonstrated by post-mortem examination of brains and peripheral tissues of patients with PD. Furthermore, the role of oxidative stress as a major contributing factor for mitochondrial dysfunction and compromised bioenergetic performance is now well established.

The brain accounts for a large amount of the energy consumption in humans. For only 2% of body weight, the brain consumes 20% of the oxygen and 25% of available glucose. Energy is generated via oxidative phosphorylation which involves the multistage electron transport chain across the inner mitochondrial membrane. Oxidative phosphorylation also generates reactive oxygen species (ROS) such as superoxide and hydrogen peroxide which, if not immediately neutralised, can cause damage to the mitochondria in which they are produced. This makes neurons in the brain particularly susceptible to both oxidative stress and energy deficits.

Chronic oxidative stress develops when ROS and RNS production exceeds the capacity of the cell's antioxidant defence system to rapidly neutralise them. Under normal conditions, Nrf2, the master regulator of redox homeostasis, constantly monitors ROS and activates the glutathione and thioredoxin systems to protect mitochondria from ROS damage. In dopaminergic neurons of PD brains, there is a wealth of evidence that this protection is defective and that it is the underlying condition driving cellular dysfunction in Parkinson's disease.

This is evidenced by increased levels of oxidised lipids, proteins and DNA, and decreased levels of reduced GSH in the *substantia nigra* of PD patients. Impairment of Complex 1 (NADH ubiquinone oxidoreductase) of the electron transport chain is a common feature of mitochondria isolated from PD patients. Loss of Complex 1 also leads to increased ROS production which amplifies mitochondrial dysfunction and creates a self-sustaining vicious circle. Magnetic Resonance Spectrometry *in vivo* has revealed that mitochondrial dysfunction is not restricted to the *substantia nigra,* but can occur in almost all regions of the brains of Parkinson's disease patients. Complex I is reported to be reduced by about 30% in the SNc and frontal cortex of Parkinson's disease patients at autopsy. Mitochondria in dopaminergic neuron synapses are more susceptible to complex 1 impairment than their counterparts in the neuron body.

Persistent fatigue, a sensation of global exhaustion unrelated to physical effort, is one of the earliest and most common symptoms reported by Parkinson's disease patients, often occurring well before diagnosis and remaining throughout its progression. Fatigue has a major impact on quality of life of PD patients, but remains one of the least documented and least researched symptoms of PD. Fatigue is also a hallmark symptom of mitochondrial disease. Markers of elevated oxidative stress and mitochondrial dysfunction correlate with disease severity of patients diagnosed with Chronic Fatigue Syndrome. For these reasons, fatigue in Parkinson's disease would appear to be due to an energy supply deficit rather than excessive demand.

Given the wealth of experimental data relating oxidative stress to mitochondrial dysfunction and compromised energy production in DA neurons, the omnipresence of fatigue reported by Parkinson's disease patients is unsurprising. The attenuation of fatigue by the participants in the broccoli seed tea experiment is consistent with the hypothesis that upregulating the Nrf2/ARE pathway and neutralising oxidative stress could attenuate mitochondrial dysfunction and restore normal energy production in neurons. The relative rapidity of the effect is consistent with the dynamics of mitochondrial regeneration.

The ability of sulforaphane to upregulate Nrf2 and activate the antioxidant response (ARE) defence processes is well established. Activation of the Nrf2/ARE pathway to neutralise oxidative stress in mitochondria and restore energy production is therefore a plausible interpretation of the impact of sulforaphane on non-motor symptoms of Parkinson's disease patients in this experiment. These observations remain to be confirmed by more rigorous studies specifically targetting oxidative stress in mitochondria of dopaminergic neurons via the activation of the Nrf2 pathway.

A theory for PD based on a cascade of 2 mechanisms

If the above hypothesis is correct, then it would appear that Parkinson's disease progresses via a cascade of 2 distinct mechanisms.

Step 1: a progressive reduction in mitochondrial energy production due to oxidative stress.

With increasing redox imbalance, oxidative stress damages mitochondria in highly-exposed neurons. This impairs the Complex 1 enzyme in mitochondria which is an essential enzyme in the process to make energy from glucose and oxygen. Reduction in Complex 1 automatically creates more ROS and sustains a vicious circle which amplifies the process. These neurons suffer an acquired but reversible version of chronic mitochondrial dysfunction through oxidative stress. The hallmark symptom of mitochondrial dysfunction is fatigue, a common non-motor symptom of Parkinson's disease. Dopaminergic neurons are among the most highly exposed because of their high energy demands, but other neuron types are also very likely to be affected.

Step 2: energy deficient DA neurons cannot sustain their normal dopamine production.

As their energy supply declines, an increasing number of DA neurons become less productive, dormant. Some may eventually die. Dopamine availability then declines below the critical threshold for normal motor function, causing the appearance of motor symptoms. Step 1 and step 2 will progress in parallel as the disease advances.

Implications and perspectives

The results of the broccoli seed tea experiment suggest that the cause of non-motor symptoms may be at least partially reversible. Reversing this first step will not automatically correct the damage already done downstream especially if it is at an advanced stage, but by differentiating between the two mechanisms, each problem should be easier to resolve.

This cascade theory for Parkinson's disease implies that 2 distinct mechanisms are involved. Both of these mechanisms need to be investigated in the quest for a global therapy for Parkinson's disease. For decades, the cause of the disease has been ignored and the only response has been to provide medication to replace reduced dopamine production.

The theory that up to 70% of dopamine-producing neurons are dead at the time of diagnosis needs to be revisited. The possibility that a significant proportion of them may simply be powered down or dormant for lack of available mitochondrial energy cannot be dismissed. It is of course possible that part of the recovery from fatigue and other symptoms noted here, could be due to improved energy production in neurons other than those involved in dopamine production. Both of these possibilities require further investigation.

A disease which progresses by 2 distinct mechanisms requires a therapeutic approach to address both steps. Current therapies only address the dopamine deficit which is responsible for motor symptoms of Parkinson's disease. There is a real urgency to respond to mitochondrial dysfunction and the energy deficit acquired through oxidative stress to Complex 1 enzymes in neurons of all types.

The current therapy of dopamine replacement is almost universally directed at attenuating motor symptoms whereas persistent fatigue, one of the most common and debilitating symptoms of Parkinson's disease is ignored. A therapy to resolve fatigue would considerably improve the quality of life of many Parkinson's disease patients.

For more information on the scientific rationale of this experiment, see:

1) https://patientresearcher.com/
2) Role of the transcription factor Nrf2 and Redox Balance in Parkinson's Disease
Albert F. Wright, ResearchGate, September 2020

References

Guo, Chunyan et al. “Oxidative stress, mitochondrial damage and neurodegenerative diseases.” *Neural regeneration research* vol. 8,21 (2013): 2003-14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4145906/

Claudia Bento-Pereira, Albena T. Dinkova-Kostova Activation of transcription factor Nrf2 to counteract mitochondrial dysfunction in Parkinson's disease. Medicinal Research Reviews, 20 July 2020. https://doi.org/10.1002/med.21714

Jazwa A, Rojo AI, Innamorato NG, Hesse M, Fernández-Ruiz J, and Cuadrado A (2011) Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism. Antioxid Redox Signal 14:2347–2360. CrossRef PubMed, doi.org/10.1089/ars.2010.3731

Johnson, Delinda A, and Jeffrey A Johnson. Nrf2, a therapeutic target for the treatment of neurodegenerative diseases. Free radical biology & medicine vol. 88,Pt B (2015): 253-267. doi: 10.1016/j.freeradbiomed.2015.07.147

Dinkova-Kostova, Albena T et al. The role of Nrf2 signalling in counteracting neurodegenerative diseases. FEBS J. 2018 Oct; 285(19): 3576–3590. doi: 10.1111/febs.14379

Yagishita Y, Fahey JW, Dinkova-Kostova AT, Kensler TW. Broccoli or Sulforaphane: Is It the Source or Dose That Matters? Molecules. 2019 Oct 6;24(19). pii: E3593. doi:10.3390/molecules24193593

Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, de la Fuente-Fernández R, Phillips AG, Stoessl AJ. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen Psychiatry. 2010 Aug;67(8):857-65. doi:10.1001/archgenpsychiatry.2010.88, PMID: 20679593

Morris, G., & Berk, M. (2015). The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. *BMC medicine*, *13*, 68. doi: 10.1186/s12916-015-0310-y PMID: 25889215

Morris, G., Walder, K.R., Berk, M. *et al.* The interplay between oxidative stress and bioenergetic failure in neuropsychiatric illnesses: can we explain it and can we treat it?. *Mol Biol Rep* **47,** 5587–5620 (2020). https://doi.org/10.1007/s11033-020-05590-5

Perier C, Vila M. Mitochondrial biology and Parkinson's disease. Cold Spring Harb Perspect Med. 2012 Feb;2(2):a009332. PMC3281591 , doi: 10.1101/cshperspect.a009332

Ciccone, Sarah et al. “Parkinson's disease: a complex interplay of mitochondrial DNA alterations and oxidative stress.” *International journal of molecular sciences* vol. 14,2 2388-409. 24 Jan. 2013, PMC3587993 , doi: 10.3390/ijms14022388

Zhou C, Huang Y, Przedborski S. Oxidative stress in Parkinson’s disease: a mechanism of pathogenic and therapeutic significance. Ann N Y Acad Sci. 2008;1147:93–104. PMC2745097 , PMID: 19076434 doi: 10.1196/annals.1427.023

Zeevalk GD, Razmpour R, Bernard LP. Glutathione and Parkinson’s disease: is this the elephant in the room? Biomed Pharmacother. 2008;62:236–49. PMID: **18400456** , doi: 10.1016/j.biopha.2008.01.017

Keeney PM, Xie J, Capaldi RA, Bennett Jr JP. Parkinson’s disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. J Neurosci. 2006;26:5256–64. PMCID: PMC6674236, doi: 10.1523/JNEUROSCI.0984-06.2006

Rango M, Bonifati C, Bresolin N. Parkinson’s disease and brain mitochondrial dysfunction: a functional phosphorus magnetic resonance spectroscopy study. J Cereb Blood Flow Metab. 2006;26:283–90. PMID: **16094320** , doi: 10.1038/sj.jcbfm.9600192

Exner, N., Lutz, A.K., Haass, C. and Winklhofer, K.F. (2012), Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. The EMBO Journal, 31: 3038-3062. https://doi.org/10.1038/emboj.2012.170

Esteras, Noemí et al. “Nrf2 activation in the treatment of neurodegenerative diseases: a focus on its role in mitochondrial bioenergetics and function.” *Biological chemistry* vol. 397,5 (2016): 383-400. PMID: **26812787,** doi: 10.1515/hsz-2015-0295

Dinkova-Kostova, Albena T, and Andrey Y Abramov. “The emerging role of Nrf2 in mitochondrial function.” *Free radical biology & medicine* vol. 88,Pt B (2015): 179-188. PMC4726722, doi: 10.1016/j.freeradbiomed.2015.04.036

Filler, Kristin et al. “Association of Mitochondrial Dysfunction and Fatigue: A Review of the Literature.” *BBA clinical* vol. 1 (2014): 12-23. PMC4136529, doi: 10.1016/j.bbacli.2014.04.001

Siciliano, M., Trojano, L., Santangelo, G., De Micco, R., Tedeschi, G. and Tessitore, A. (2018), Fatigue in Parkinson's disease: A systematic review and meta-analysis. Mov Disord., 33: 1712-1723. https://doi.org/10.1002/mds.27461