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Retinal function in the etiology of Parkinson's disease

The eyes are involved in the genesis and progression of Parkinson's disease

A novel treatment may be more effective in treating Parkinson's via the eyes

Abstract

Deteriorating Retinal function has been shown to be involved in the etiology of Parkinson's disease (PD).[1,2] However, recent work suggests that PD may be caused or worsened by retinal deterioration. Research also shows that treating Parkinson's with light through the eye not only causes symptomatic improvement, but may also be disease modifying.[3] Animal studies have shown light to be more effective than dopamine or other medications, and preliminary human studies have shown similar responses. A pivotal, double-blind study is currently underway to verify these findings.

Retinal Dopimenergic Function: Normal vs. Parkinson's

In order to understand how retinal deterioration is related to Parkinson's, it is important to review normal retinal function and how it is compromised in Parkinson's disease. In normal eyes, daytime signaling to the brain is mediated by the cone-retinal ganglion system.[4] Although rods and cones are both involved in dopamine (DA) synthesis and release, DA is light activated and most dominantly modulated by cones during the day, while melatonin synthesis is responsible for cone inactivation at night.

Melatonin inhibits dopamine-cone function and activates rods.[5] For example, in response to nighttime darkness, dopamine is replaced by melatonin. This inactivates the cones as well as the melanopsin/ganglion system. As a result the eyes become dark adapted, allowing for night vison. This circadian modulation between daytime dopamine and nighttime melatonin in the retina allows for vision in bright sunlight as well as in near total darkness.

However, this process is compromised in PD. Studies show that the dopamine neurons in eyes of Parkinson's patients are damaged,[6,7,8] and that melatonin becomes dominant in the absence of dopamine.[9] This may explain why many Parkinson's sufferers are permanently dark adapted and tend to avoid bright light.[10,11]

Circadian Impairment

Altered dopamine and melatonin modulation have a negative impact beyond vision impairment. Retinal dopamine is essential for circadian regulation as well as alertness and visual signaling to the brain.[4,12] In a dark adapted state, these functions are likely compromised, which may help to explain why PD patients suffer from sleep and mood problems.[13]

Retina and Substantia Nigra Interdependence

It may be that retinal dopamine loss causes more than circadian and visual problems. Reports show an association between deteriorating dopaminergic activity in the brain concurrent with the loss of dopaminergic activity in the eye.[6,14,15] Only recently has this relationship been viewed as interdependent or causal.[7]

A recent study examined the question as to whether the brain and the eye are concurrently insulted by outside influences, or whether damage to one site causes damage in the other.[16] In this experiment, only the substantia nigra and medial forebrain bundle of one hemisphere were lesioned by 6-hydroxydopamine (6-OHDA). Within three weeks, the majority of dopamine neurons in the contralateral retina were destroyed, while the ipsilateral retina was not as affected. This suggests that a neural pathway exists between the eye and the motor center of the brain and that these sites function interdependently. Because daytime retinal melatonin increased as well, the authors concluded that increased retinal melatonin probably is associated with the progression of Parkinson's disease.

Retinal Damage May cause Parkinsonism

Additional studies have been done to assess whether damage to the eye causes damage to the brain. While it is known that substances such as 6-OHDA and paraquat cause parkinsonism, it is important to note that they are molecularly too large to pass through the blood-brain barrier. However, they are absorbed by the eye through the blood-retinal barrier.[17,18,19,20] This suggests that these toxins may first be damaging the eye, which in turn causes damage to the brain.

To further elucidate this relationship, 6-OHDA, 1-methyl-4-phenyl-1-2,3,6-tetrahydropyridine (MPTP), paraquat, and rotenone were injected in rats' eyes in quantities that were too small to diffuse into the brain.[21] In each case, the animals developed parkinsonian symptoms the same as those obtained by directly injecting these toxins into the substantia nigra. The fact that damage to the dopamine neurons in the eye causes parkinsonism, suggests that the eye is involved in the etiology and progression of the disease.

Antagonistic Nature of Dopamine and Melatonin

Higher melatonin levels are also associated with a Parkinsonian state, primarily because melatonin and dopamine act in functional opposition, and melatonin inhibits dopamine.[22] As shown earlier, dopamine destruction in the substantia nigra not only causes dopamine destruction in the retina, but also an increase in retinal melatonin. Animal studies have shown that retinal microinjections of melatonin worsened PD.[22] Melatonin is naturally released in darkness. Constant darkness and enucleation of the eyes also worsened PD.[23] These studies suggest that the increase of retinal melatonin is responsible for the dark adapted state in Parkinson's disease, and that retinal melatonin may inhibit the cone-ganglion signaling pathway, causing PD to become worse.

Light Inhibits Melatonin, Activates Dopamine

Thus if this negative imbalance with retinal melatonin and dopamine could be rectified, it should have beneficial effects on Parkinson's disease. In animal studies, microinjections of dopamine were introduced into the eye in Parkinsonian rats in an effort to counter the effect of increased retinal melatonin. Although the quantity of dopamine was too small to diffuse into the brain, the animals experienced symptom recovery.[21]

Light Produces Twofold Response

Similar effects were found with agents that blocked melatonin.[24,25] Light is known to suppress melatonin and activate dopamine.[4,5,12] When light was used, the animals recovered twice as quickly as compared to dopamine or melatonin antagonists.[22] Light is essential for healthy dopamine function, eye survival and growth.[4] These facts suggest that light may elicit a reparative response beyond dopamine activation or melatonin suppression.

Human Light Therapy Investigations

The success with light in animal studies, together with the non-invasive and non-significant risk profile of light therapy, justified its application in humans. To date, five studies have been published on light therapy in Parkinson's.[3,26,27,28,29] These studies show significant improvements in both motor and non-motor symptoms, with the 129 patient retrospective analysis showing the most significant and longest term improvement.[3] In this study, the average binned data for each subject was 43 months and compared 98 subjects on light therapy to 31 control patients. The improvement for the light therapy group was significant on nearly all types of symptoms.

One study comparing light therapy and Doxepin, showed some improvement in sleep with light but no effect on motor function.[29] This is not surprising, as it used morning light with some but evening light with other patients. Previous studies showed differential responses to morning vs. evening light.[3,27,28] Thus the response of each group may have had a cancelling effect.

One additional study employed total sleep deprivation (TSD) for 24 hours with Parkinson's patients suffering from depression.[30] A marked decrease in depression was observed along with improvements in tremor, rigidity and bradykinesia. Although several mechanisms were postulated, the authors could not rule out the prolonged exposure to light as a basis for the therapeutic effect.

Tolerance to Light Therapy

In human studies, light therapy was reported to be very well tolerated with only temporary, benign side effects. The side effect profile in Parkinson's light therapy studies is consistent with other light therapy studies.[31,32] No serious adverse event or long term side effects have been reported with light therapy. In addition, long-term ophthalmological reviews for up to 6 years have shown no ocular damage.[33]

Time of Day Aspects of Light Administration

Because light therapy affects the circadian system, it is logical to assume that there are circadian aspects of Parkinson's, and thus Parkinson's may be better treated with light at a specific time of day. Morning light has been effective in treating certain depression and sleep problems,[34,35] and it would seem logical to administer morning light to Parkinson's patients as well. In a small double-blind study employing morning light,[38] mood

and tremor improved but without a discernible effect on sleep.

However, morning light may not improve sleep, as Parkinson's patients may be phase advanced and thus require evening light exposure.[27,36,37,38] In a larger longitudinal analysis, evening light not only improved mood and sleep, but tremor, rigidity, and bradykinesia as well.[3] As individual biological clocks differ, some have suggested applying morning or evening light therapy based on the patient's chronotype.[13] However, the Doxepin study applied a similar method with inconsistent results.[29] The best evidence to date shows consistent improvement on both motor and non-motor symptoms with evening light administration.

Duration of Exposure

Early white light therapy studies for depression and sleep employed light therapy for up to 2½ hours at a time and at lower intensities than the typically used level of 10,000 lux.[39,40] Over time, a dose response relationship with light was discovered such that light at 10,000 lux required only 30 minute durations.[41,42] A similar phenomenon with Parkinson's has been found, with improved response to ~3,000 – 4,000 lux of bright light performing better than 1,500 lux. [3,37] However, Parkinson's patients tend to be dark adapted or photophobic,[10] and thus they may not tolerate high intensities of 10,000 lux.

Research in Parkinson's disease and light therapy is ongoing, and the systems affected by light are not as well elucidated. To date, the most significant long-term response to light has been obtained with 1 hour durations instead of 30 minutes. However, future dose response studies may find shorter durations to be effective.

Rapidity of Response

Both short and long-term studies have suggested light therapy to be effective in treating the primary symptoms of Parkinson's disease. The only double-blind study was short-term (15 days), and showed nominal but significant improvements in sleep, mood and tremor, but not rigidity or bradykinesia.[38]

Additional studies used longer durations of 6-plus months to experiment with different variables of light administration. One longer term evaluation used a control group, but did not consistently apply light therapy (10 sessions over 6 months).[26] This study used morning light and found improvements in sleep, mood and some motor symptoms, but not tremor. Another longer term open label analysis found further improvements with evening light, except for tremor.[37] Follow-up work with evening light increased the light intensity from 1,500 lux to 4,000 – 6,000 lux and found improvement in tremor, suggesting a dose response with light therapy.[3]

The longest term analysis compared 129 PD patients with binned data averaging nearly 4 years.[3] This open label study's methodology was refined from the findings of the previous studies. This study used a control (dopamine replacement medication without light therapy) compared to an active group receiving both light therapy and dopamine replacement medication. This study is the best evidence to date for the rapidity of response. In general, 5 months was necessary to demonstrate a sustained improvement in primary motor symptoms, including tremor, rigidity and bradykinesia. However, secondary symptoms improved more rapidly. Sustained significant differences in sleep, mood, anxiety, etc., occurred within the first few months.

Polychromatic vs. Specific Bandwidth Light

In the past, light therapy studies employed broad bandwidth, polychromatic fluorescent light at intensities ranging from 10,000 to 12,000 lux. However, recent studies have demonstrated that a specific bandwidth of 470 nm blue light is important for regulating the circadian and alerting pathways in the brain.[43,44,45] The disadvantages to using polychromatic light are threefold: 1) polychromatic light produces very little 470 nm light, 2) polychromatic lights vary widely as to their spectral emissions, and 3) the spectral output of polychromatic light varies over time. Thus polychromatic lights are generally less efficient than specific bandwidth technology, and some polychromatic lights may be less effective than others.

Finally, 10,000 lux intensity also produces glare and related side effects, such as headaches, nausea, jitteriness, eyestrain, etc.[31] Optimizing light therapy with low intensity 470 nm light for Seasonal Affective Disorder was found to be effective with a favorable side effect profile.[46,47,48,49] Thus optimizing specific band-widths and intensities of light may improve light therapy of PD while reducing associated side effects.

During a several year, retrospective analysis, investigators noticed a differential response depending on the spectral properties of the light therapy devices used. Patients responded better to certain light boxes and not as well to others. When checked, the spectral properties of these light boxes varied greatly. Thus the authors cautioned against the ad hoc use of available light therapy devices for Parkinson's disease.[3]

This observation led to a number of unpublished pilot studies to determine a more optimal light device for Parkinson's.[50,51,52] These studies utilized various wavelengths of light including (~464 nm), (~520 – 570 nm), and (575 – 650 nm), and suggest that different wavelengths have different effects upon the therapeutic response. These studies showed that Parkinson's patients may respond better to action spectra similar to the action spectrum for circadian regulation. However, it became apparent that more than one specific bandwidth of light was essential for Parkinson's, and thus the resulting color is different than the action spectrum for circadian regulation.

Negative Effects of Long Wavelength Light

Additional unpublished data suggests that long-wavelength light may cause negative effects in Parkinson's disease.[51] A pilot study used a crossover design to determine the effect of specific bandwidths of light, including red light. All of the patients on red light (575 – 650 nm) responded negatively and needed to be withdrawn from the study. Because of this negative response, it was recommended that red light should be reduced as much as possible.

Why Long wavelength light may aggravate Parkinson's

Ganglion cells in the inner retina contain the photopigment melanopsin which is the primary regulator of melatonin production. Because melanopsin lies in the inner layer of the retina, it is not regenerated by the retinal epithelium as are rods and cones. Thus melanopsin by nature is bistable; being activated by short wavelength light and regenerated by long wavelength light. Melanopsin produces an 'on' response (suppressing melatonin) in reaction to short wavelength light, and may produce an 'off' response (allowing melatonin) in reaction to long wavelengths.[53]

Phototherapy vs. Light therapy

As research in light therapy has progressed, it is evident that lower intensities, combined with specific bandwidths of light are more effective than conventional bright light therapy. Using specific bandwidths allows the overall intensity of light to be dramatically reduced, while detrimental wavelengths can be filtered or eliminated. Thus, specialized phototherapy, is a more appropriate application for treating Parkinson's disease.

Applicability to the Spectramax™ Phototherapy Lamp

After reviewing this data, PhotoPharmics, Inc. developed the Spectramax™ phototherapy lamp to emit the effective spectra while eliminating the red. The intensities found effective in prior studies were applied to Spectramax™, and the overall intensity is approximately 1/10th that of traditional bright light therapy (~1,000 lux or 250 – 500 µW/cm^2/sec). This level of irradiance is comparable with the low-intensity, specialized light therapy devices that have been reported to be effective for Seasonal Affective Disorder. This lower intensity resulted in a more favorable tolerance of the light therapy device and a reduction in adverse side effects such as headaches and dizziness caused by glare. In an unpublished pilot study over 6 months, patients treated with a prototype phototherapy lamp producing the Spectramax™ light output responded as well as or better than the polychromatic light condition.[52]

Photobiological Safety of Spectramax

The Spectramax™ Lamp has been independently certified as belonging to Risk Group-0, i.e. no risk, under two international safety and performance standards; IEC/EN 62471, Photobiological Safety of Lamps and Lamp Systems, and the Medical Device Standard IEC 60601-2-57, Particular Requirements for the Basic Safety and Essential Performance of Non-Laser Light Equipment.

Conclusion

Parkinson's sufferers have deteriorated dopamine neurons, both in the brain as well as in the eye. New evidence suggests that these sites may be inter-dependent, and that deterioration of the retinal dopaminergic system may contribute to or cause Parkinson's disease.

Dopamine is both activated and regulated by light. Melatonin is antagonistic to dopamine and is suppressed by light. Light administration has been effective in treating Parkinson's, both in animal and human studies. Five human studies have been conducted, showing that strategically applied light therapy improves PD symptoms. The largest of these studies suggests that

light therapy may have a disease modifying effect. Both published and unpublished studies also show that as with other disorders, Parkinson's disease's response to light therapy is dependent on both the intensity and spectral composition of light, and that patients may respond negatively to longer wavelength light.

Using Spectramax for Parkinson's is an attractive treatment option because its effects should be realized within a few months, without negative side effects. A pivotal, double-blind study is currently underway to further validate these earlier findings. Results from this study should be available in 2016.

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