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Seasonality, suicidality and melatonin

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Seasonality of suicidal behavior has been investigated regarding both neurobiological and climatic factors, as well as psychopathological and social aspects. Most of the studies detected peaks in late spring and troughs in the winter. Several lines of evidence evaluated the role of extended periods of light associated with probability of suicides whereas others summarize the alterations of melatonin excretion and its seasonal variation along with seasonal distribution of psychiatric disorders. The purpose of this paper is to provide an overview of studies attempted to reach an explanatory model of underlying pathophysiology of melatonin in the pathogenesis of seasonal variation in suicidality. There is argument on the interconnection between suicide rates and weather factors. However, an inverse pattern of melatonin levels and the seasonal peak in suicides was observed. These findings suggest that sunlight exposure along with a wide spectrum of other factors may explain the aetiopathogenesis of suicidal behavior.

Key words: seasonality, suicidal behavior, melatonin, depressive symptoms, genetics variations, sunlight

Seasonality of suicidal behaviour

Suicidal behavior is a universal human behavior and constitutes a major public, as well as mental health problem. A low rate of both completed and attempted suicides over the last half-century was observed in Greece. This low suicidal rate is attributed to social and cultural parameters, such as close family ties and easy discharge of anger.[1–7] Many studies demonstrated seasonal influence on suicides in countries of North and South hemisphere and how they varied with latitude.[8–13] Most of them found clearly present a spring-time peak especially in the regions far from the equator (more pronounced differences in day length along the year). Other investigators emphasized the same annual pattern with special reference to suicides committed by males and by violent methods.[14–17] A seasonal variation of mainly male committed suicides was observed in Greece. Suicidality by violent methods for individuals above the age of 45 peaks in early May. As for the method, suicide by hanging peaks in June and by shooting in April.[18] Moreover, there is evidence that male psychiatric patients who attempt suicide by violent methods may have a dysfunction of the

hypothalamic-pituitary-gonadal axis at the hypothalamic-pituitary level.[19]

The season of birth was investigated in major depressive patients (and further suicidality). No effect from the season of birth was found in suicidal attempters with major depression whereas the study confirms the effect of seasonality of birth on patients suffering from specific types of depression.[20]

Weather factors, not necessarily considered as periodic changes, have shown a positive relationship to suicide rates; findings mainly supporting the function of photoperiod as the most serious impact on suicidal behavior.[21–23] Furthermore, several publications reported associations between monthly temperature, humidity grade, wind velocities, lunar phases, rainfall mean, time of the day and suicidal acts.[14,21,24–26] Distribution of attempted suicides may show a seasonal pattern as well, while there is also literature focused on suicidality of certain subgroups, such as alcoholics, workers exposed to electromagnetic fields and influence by ozone and air pollution.[27–30] The above-mentioned studies indicate a possible interconnection between seasonal pattern of suicidal acts and alterations in neurotransmitter systems which could trigger impulsivity, pessimism and aggression. These traits may implicated in the susceptibility to suicide attempts. Nevertheless, various limitations exist, concerning data collected from urban/rural regions, marital status and other sociological parameters that interfere with the interpretation of results.

Melatonin, other biological factors and socialdemographic parameters

Melatonin is produced by the pineal gland exclusively during night-time and synchronized by the suprachiasmatic nucleus. Since its excretion occurs via stimulation of beta-adrenoreceptors, is considered as an index for noradrenergic function. Two studies[31,32] investigated the adrenoceptor sensitivity in depression (and further suicidality) by using melatonin response. In the first one, administration of clonidine (a central acting α2 adrenoceptor agonist) by a single oral dose of 0.15 mg, significantly reduced melatonin concentrations in depressed patients, but not in control subjects. In the second study, administration of atenolol (a peripheral β1 receptor antagonist) by an oral dose of 100 mg, strongly reduced melatonin in depressed and control subjects. The proposed metabolic pathway starts from tryptophan, which is metabolized into 5-hydroxy tryptophan (5-HTP) by tryptophan hydroxylase (TPOH); then 5-HTP forms serotonin (5-HT) by 5-HTP-decarboxylase and a third step includes acetylation (via function of another enzyme, the acetyltransferase) into N-acetylserotonin (NAS). Finally, the O-methylation of NAS forms melatonin.[33–35] A study on overnight urinary melatonin was conducted on the most geographically dispersed population in Greece. Females had higher overnight urinary melatonin values than males.[36] A seasonal bimodal pattern on melatonin excretion was observed in Greece among healthy volunteers. Bergiannaki et al[37] investigated the influence of season and the component of geomagnetic field on melatonin excretion. Peak values were observed in June and November when a high length stability, as well as low values of the vertical component of the geomagnetic field was recorded. On the other hand, in April and August-October trough values were recorder when a low daylength stability with high values of the vertical component of the geomagnetic field was combined.

The photoperiodic message can affect various parameters of the melatonin secretion; higher amplitude under a long photoperiod, higher duration of the secretion peak due to a higher night-length. Moreover, there are non-photic factors implicated in production of melatonin, such as age, gender, body mass index, geomagnetic activity, traumatic head injury and temperature. For instance, ambient temperature is inversely connected to the amplitude of the nocturnal melatonin peak and the rhythms of epiphysis metabolism decrease with age.[27,35,38–41] Among healthy individuals, night-time urinary melatonin level may reflect a genetically determined mechanism.[42] Low melatonin levels were closely related to melancholic depression.[43]

The genetic basis of suicidal behaviour

The circadian rhythmicity exerts autonomy independent to light stimulation, or even pineal function, most probably demonstrating the major role of certain clock genes and the governing function of several nuclei in CNS, such as the suprachiasmatic ones. It has been hypothesized that the genetic basis of suicidal behavior plays a complex role independently from other genetic factors predisposing to psychiatric disorders, even if these disorders are often associ-

ated with suicidality.[41] A polygenic inheritance of suicidal behavior in depressed patients with a history of suicide attempts was detected.[44] The occurrence of suicidal ideation was a familial component, stronger among males than females psychiatric patients.[45]

It is widely accepted that serotonergic dysfunction predispose to phenotypes of increased vulnerability to traits associated to suicidal behavior (as for example disturbed impulse control). Although studies have reached in many cases contradictory conclusions, many of them offer candidate genes responsible for such behavior. One of them is located on chromosome 17 expressing the 5-HT transporter. A functional polymorphism (s-allele of 5HTTLPRR) decreases the serotonin uptake by lowering the gene expression, a condition related with neuroticism. Additionally, postmortem findings in suicide victims display reduction in 5-HT transporter in the region of prefrontal ventral cortex.[46,47]

Researchers have associated the low levels in the cerebrospinal fluid of the major 5-HT metabolite (5-hydroxy-indoleacetic acid) with various psychiatric disorders including depression and suicides. A significant correlation between TPOH (limiting enzyme in the synthesis of 5-HT and possibly melatonin) and inadequate impulse control has been pointed out elsewhere, suggesting that an intron 7 polymorphism on chromosome 11 in the region of TPOH gene, plays a role in reduction of serotonin turnover. Other, functional or not, allele variants which adjust mechanisms like transporting, secretion or binding of neurohormones (including melatonin and component molecules) in serotonergic and nor-adrenergic systems have been reported.[48–52] Homozygosity for the short allele (the frequency of the C-C genotype) is significantly less frequent in unipolar affective disorder patients with a history of suicide attempt than in healthy subjects.[53]

Genetic correlates of seasonal variation in suicide-the SAD patient

Several studies attempted to reveal a correlation between endophenotypes predisposing to suicide and periodic biochemical patterns. TPOH gene's expression displays different levels of the enzyme activity during day time with an increase during night. Lower levels of plasma L-tryptophan in spring match the annual pattern for suicides. Decreased serotonin transporter binding potential, under a longer photoperiod, may offer an explanation for changes in individual's behavior, according to the expected increase of synaptic 5-HT levels.

The observation of hyperactivity of the serotonergic system in spring might seem paradoxical since we expect lower 5-HT activity during the time of higher suicide risk. Moreover, a certain subpopulation of depressed patients seems to get worse in symptoms during the late fall and winter (Seasonal Affective Disorder, SAD).[54–56]

It may be useful though to keep in mind that mechanisms, such as auto inhibition of 5-HT receptors on different locations in the brain, have been shown to affect in opposite ways the 5-HT outflow in certain brain regions.

A possible explanation interconnecting the role of photoperiod with individual's mood has been described suggesting a triggering effect of sunshine–in short term– on suicide behavior.[57] Thus, it is plausible to combine the beneficial impact of sunlight on spirits with the incidence of suicides in spring. The same report pointed out a hypothetical model for the sunshine effect in women and how it can be mediated by the hypothalamic-pituitary-adrenal axis. Petridou et al[58] confirmed the positive association between month of maximum daylight and higher relative risk for suicide, stressing the need for further investigations on how sunshine affects melatonin and melatonin affects mood regulation (not excluding the role of 5 HT and L-tryptophan in behavior changes along with sunshine dependence). The results were estimated according to data sent by 20 countries for the last 5–24 years. Investigations also exist about the role of acute changes in the luminosity, with higher turnover of 5 HT in the brain on bright days. The pathophysiology may involve traits predisposing to suicidal behavior (aggression and impulsiveness) or hormonal changes, such as suppression of melatonin due to light accompanied with lack of sleep. Bjorksten and colleagues[8] reported a significant seasonality in a total of 833 suicides during the period 1968–1995 and noted that lifestyle changes during the arctic summer may cause several disorders like psychosis, exacerbation of affective disorders and delirium either because of lack of sleep or via the pre-mentioned changes in 5 HT turnover due to increased luminosity. The theoretical model of solar radiance, in the long term acting protectively and

over a short term as a triggering factor for suicide, matches the mechanism of antidepressants which initiate a pronounced motivation into the mood before they improve the whole spectrum of depressive symptoms. It is possible thereby, that changes in the weather increase the risk of suicide mainly in individuals with specific vulnerability; even though there is no identification of a "suicide-gene", certain genes might interact with each other so as to predispose to suicidal behavior under the influential role of the photoperiodic message.

The "Low melatonin syndrome"

A described hypothetical model for a subgroup of depressed individuals involves low nocturnal melatonin levels along with: (a) abnormal dexamethasone suppression test, (b) less pronounced periodic alterations in symptoms, and (c) abnormal 24-h rhythm of cortisol.

Neither the SAD patients, nor the subgroup of patients with Low Melatonin Syndrome (LMS) follow any specific suicide seasonal pattern. However symptoms correlated with the latter, like anaedonia and lassitude may incline towards suicidal thoughts; moreover, lower levels of pineal melatonin content were found in suicide victims. Some depressed patients suffering from lassitude and profound sadness had lower melatonin levels, albeit in this study have been reported higher melatonin maximum levels in participants with suicide attempts than ones with no suicide attempt.[59]

Seasonality of melatonin levels and interaction between 5-HT and melatonin

In a sample of 32 depressed outpatients, Carvalho and colleagues noted alterations in the levels of a urinary metabolite of melatonin solely in those with severe symptoms.[38] The analyzed participants were drug-free, thus it was possible to exclude the confounding process of the cytochrome inhibition by several drugs which may alter the secretion amplitude of melatonin. Significant peak of suicides, particularly for the age group over 45, have been observed in the morning by other investigators. Still, various limitations remain, such as the factor of abnormal synchronization to the duration of photoperiod in patients who, due to their melancholic symptoms, spend less time outdoors. To make things more complicated, the day-length variations over different seasons of the year may not represent the same amount of the light exposure for different individuals and populations. Given that illuminance of 60 lux suppresses melatonin secretion, its onset seems to depend exclusively upon the timing of sleep, as far as individuals in modern life are concerned. Besides, artificial light contains less blue than natural one; considering previous observations that the spectral sensitivity for melatonin regulation is greater for the blue light, it becomes obvious that the time spending indoors with lights open contributes in a complicated, plus worthy of further understanding, way to the modulation of the circadian characteristics of behavior.[60–63]

Arendt et al[64] noted that the annual variations of serum melatonin tend towards an inverse pattern with the levels of platelet 5-HT. Moreover, the 5-HT hypothalamic content (probably representing a precursor for the production rate of melatonin) was found 180° out of phase with melatonin content. Administration of melatonin increases serotonin levels in brain regions and 5-HIAA in cerebrospinal fluid. Numerous publications described low melatonin levels in spring and suggested a close interconnection between fluctuations of the two indoleamines with a nadir in 5-HT levels in winter confirming the inverse pattern.[65–68] Among the former, one may find enough evidence to hypothesize a bidirectional interaction and data contributing to interpretations for seasonal phenomena, such as affective disorder, extraordinary impulsivity and suicidal acts.

Conclusion

The annual variation in suicide has been inversely related to the annual pattern of melatonin with a spring-peak in suicides and a spring-nadir in melatonin levels, along with seasonal changes in closely related neurotransmitter systems, mainly those of serotonin. No profound relationship has emerged among meteorological conditions and tendency to suicidal behavior. Socio-epidemiological factors need to be taken into account, while the way the intrinsic circadian system interacts with psychiatric conditions remains uncertain.[69,70] Further research regarding the aetiopathogenesis of suicide in relation to sunlight exposure and rhythmicity of melatonin activity, might lead to an explanatory model for the seasonal distribution of suicide.

Εποχιακή κατανομή, αυτοκτονικότητα και μελατονίνη

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Η εποχικότητα της αυτοκτονικής συμπεριφοράς διερευνάται σε σχέση με νευροβιολογικές, κλιματικές, ψυχοπαθολογικές και δημογραφικές παραμέτρους. Οι περισσότερες μελέτες εντοπίζουν αύξηση της αυτοκτονικότητας περί τα τέλη της άνοιξης ενώ το χειμώνα σημειώνεται μείωση. Ερευνάται ο ρόλος της παρατεταμένης ηλιοφάνειας σε συνδυασμό με την πιθανότητα για αυτοκτονία. Άλλες εργασίες εστιάζουν στις μεταβολές της έκκρισης της μελατονίνης παράλληλα με την εποχιακή κατανομή ψυχιατρικών διαταραχών. Επίσης, ειδικές υποκατηγορίες όπως παρα-αυτοκτονικές συμπεριφορές, συννοσηρότητα με αλκοόλ και επίδραση άλλων ειδικών συνθηκών (π.χ. ηλεκτρομαγνητικά κύματα, ατμοσφαιρική μόλυνση κ.ά.) μελετώνται ως προς την εποχικότητα της αυτοκτονικότητας ή/και σε σχέση με την έκκριση μελατονίνης. Ο σκοπός του άρθρου συνίσταται σε μια γενική θεώρηση μελετών που επιχειρούν να προσεγγίσουν ένα επεξηγηματικό μοντέλο σχετικά με την παθοφυσιολογία που μπορεί να υφίσταται στην έκκριση νευροδιαβιβαστών και ειδικότερα της μελατονίνης (ή των πρόδρομων αυτής ουσιών) και πως αυτή πιθανώς συμβάλλει στην ανισοκατανομή των αυτοκτονιών κατά τις εποχές του έτους. Ακόμα, γίνεται αναφορά σε μελέτες που αναζήτησαν σχέση μεταξύ μετεωρολογικών δεδομένων (π.χ. ηλιοφάνεια) και διαταραχών της συμπεριφοράς. Εντοπίστηκε σημαντικός αριθμός γενετικών μελετών που επιχειρούν να διακρίνουν στοιχεία συμπεριφοράς που ενέχουν κίνδυνο εκδήλωσης αυτοκαταστροφικότητας και ελέγχονται γονιδιακά. Αναφορά γίνεται σε υποκατηγορίες της κατάθλιψης, όπως η «εποχιακή κατάθλιψη» και το «σύνδρομο χαμηλής μελατονίνης» που έχει υποτεθεί από ορισμένους ερευνητές ότι σχετίζονται με ρυθμικές μεταπτώσεις στη διάθεση. Δεν έχει εντοπιστεί σαφής συσχέτιση της αυτοκτονίας με συγκεκριμένα καιρικά φαινόμενα. Εξάλλου, το εάν τελικά, πώς και σε ποιο βαθμό απορρυθμίζεται το κιρκαδιανό σύστημα σε άτομα που νοσούν από ψυχιατρικές διαταραχές, αποτελεί, ακόμη, αναπάντητο ερώτημα. Ωστόσο, έχει παρατηρηθεί ότι την εποχή που σημειώνεται αύξηση της συχνότητας αυτοκαταστροφικών συμπεριφορών υπάρχει αντίστοιχα μείωση στα επίπεδα μελατονίνης. Βέβαια, τα επίπεδα μελατονίνης έχουν στενή σχέση με τη σεροτονίνη που είναι διαθέσιμη στο ΚΝΣ και με την έκθεση στο ηλιακό (και όχι μόνο) φως. Τα παραπάνω δεδομένα μαζί με ένα ευρύ φάσμα άλλων ποικίλλων παραγόντων ίσως προσφέρουν στο μέλλον περισσότερες διευκρινήσεις για την αιτιοπαθογένεια και την πρόληψη των αυτοκαταστροφικών συμπεριφορών.

Λέξεις ευρετηρίου: εποχικότητα, αυτοκτονική συμπεριφορά, μελατονίνη, καταθλιπτικά συμπτώματα, γενετικές διαφοροποιήσεις, ηλιοφάνεια

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