Melatonin Counteracts Cholesterol's Effects on Lipid Membrane Structure

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The cell membrane plays an important role in amyloid toxicity in relation to Alzheimer's disease (1,2). The membrane's composition and the inclusion of small molecules, such as melatonin and cholesterol, may alter the membrane's structure and physical properties, affecting its interaction with amyloid peptides. Both melatonin and cholesterol have been linked to amyloid toxicity. Cholesterol is a well known sterol and plays an important role in lipid raft formation, while it has been shown to enhance the amyloid binding and fibril formation when present in a membrane (3). Melatonin - a pineal hormone that is produced in the human brain during sleep and that sets the sleep-wake cycle (and circadian rhythm) (4) - has been in contrary to cholesterol shown to have a protective role against amyloid toxicity (5,6). Nevertheless, the underlying molecular mechanism of this protection is still not well understood.

Earlier we studied effect of melatonin and cholesterol on the structure of DPPC and DOPC lipid membrane, and showed that melatonin reduces membrane thickness and induces disorder in lipid tails (7). Here we have studied the non-specific interaction of melatonin and cholesterol with a model lipid membrane prepared of dioleoyl-sn-glycero-3-phosphocholine (DOPC), where cholesterol and melatonin were both present in lipid membrane at various proportions (Figure 1). We used small-angle neutron diffraction (SAND) from the stacks of oriented lipid multilayers to elucidate the structure of membranes (8), and in order to determine the effects of melatonin and cholesterol. From the present study we conclude that melatonin counteracts the effect cholesterol has on the structure of lipid membrane. Specifically, the additional incorporation of melatonin results in membrane thinning, despite and in stark contrast to the increase in membrane thickness induced by increasing concentration of cholesterol. This very different response of membrane thickness to cholesterol and melatonin and their mixtures may help to understand their relation to amyloid toxicity and to clarify the role of cholesterol and melatonin in this process.

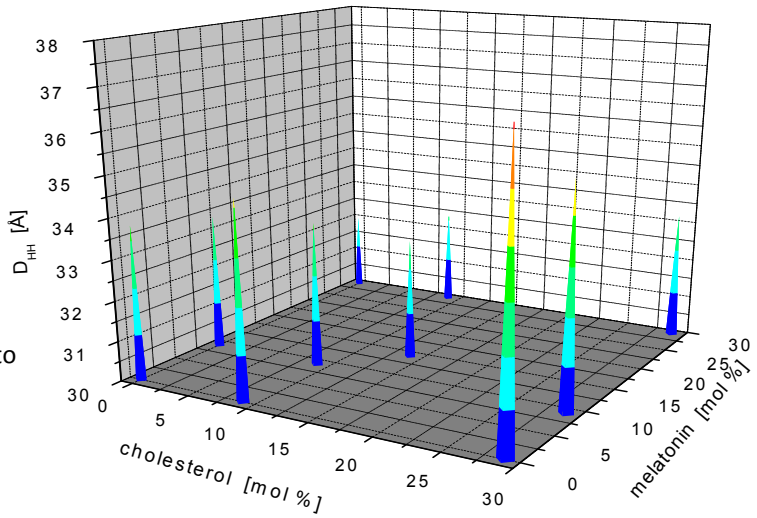

Figure 1 The lipid headgroup-to-headgroup distance (D_{HH}) as a measure of DOPC bilayer thickness. The graph shows an increase of DHH with the increasing cholesterol, while counteracting effect is caused by the addition of melatonin.

References

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