

# Neurobiology of Lipids

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*opening note commentary*

## THE EMERGING NEUROBIOLOGY OF CHOLESTEROL

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**A**lthough cholesterol gets a bad press as a cause of vascular disease, it is, of course, an essential component of all mammalian cells. In neurobiology, three quite different roles of cholesterol can be discerned: as a structural component of the plasma membranes of neurones and glia; as the precursor for a cascade of steroidal hormones and mediators affecting both genomic and non-genomic processes in neurones; and as a direct modulator of the functions of certain plasma membrane proteins.

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### CHOLESTEROL AND CELL MEMBRANE STRUCTURE

Much of our current understanding of the structural role of cholesterol in cell membranes stems from work since the early 1970s elaborating the fluid mosaic model.<sup>1</sup> Among the most recent developments is the involvement of cholesterol in the clustering of particular lipids within the membrane bilayer to form rafts which, in turn, influence the distribution of proteins within the membrane.<sup>2</sup>

### CHOLESTEROL AS A STEROIDAL PRECURSOR

In contrast, the essential precursor role of cholesterol in the biosynthesis of steroidal mediators generates rather little active interest since the availability of cholesterol appears not to be a

rate-limiting. In this area of neurobiology, it is the metabolites of cholesterol and particularly their non-genomic actions that have added a new dimension to our understanding of neuronal modulation and continue to attract attention.<sup>3</sup>

### MODULATION OF MEMBRANE PROTEINS BY CHOLESTEROL

Less widely known, in part due to lack of a comprehensive review, is the third of the roles mentioned above to which I particularly wish to draw attention. This is concerned with the lipid structure of the plasma membrane of cells and its influence on the functioning of proteins that reside in the plasma membrane. The modulatory influences may be due to individual lipids and/or to the membrane environment as a whole. Research in this area has been rather spasmodic and seems to have arisen largely as a series of side issues to primary interests in particular protein families. Nevertheless, sufficient information has now accumulated to establish the potential importance of such protein/lipid interactions.

In the early 1980s, there was a flurry of activity involving a variety of membrane proteins. Interpretations of the protein/lipid interactions observed were strongly influenced by the considerable body of in-depth work that had been published on the biophysical properties of lipid bilayers and biological membranes. Thus, membrane fluidity was the prime mechanism considered for lipid modulation of protein function. However, several authors who manipulated membrane cholesterol levels to achieve changes in fluidity recognised the possibility that cholesterol itself might exert additional direct effects. Examples include studies on adenylate cyclase,<sup>4</sup>

GABA uptake transporters<sup>5</sup> and the nicotinic acetylcholine receptor of *Torpedo*.<sup>6</sup>

Continued interest in this aspect of nicotinic acetylcholine receptor regulation<sup>7,8</sup> further strengthened the evidence in support of distinctive influences by membrane fluidity and direct cholesterol-protein interactions, including the dependence of the latter on specific phospholipids. In the meantime, other receptor proteins were studied with regard to mechanisms of modulation by membrane cholesterol, including the visual pigment rhodopsin,<sup>9</sup> oxytocin and cholecystokinin receptors<sup>10</sup> and the GABA<sub>A</sub> receptor.<sup>11,12,13</sup> A recent analogous study on multidrug resistance P-glycoprotein<sup>14</sup> demonstrated a wider applicability of the phenomenon.

### MANIPULATION OF MEMBRANE CHOLESTEROL IN VIVO

The free cholesterol in cells is located almost entirely in the plasma membrane. It has proved quite easy to manipulate the cholesterol content *in vitro* and a variety of methods is described in the foregoing references. It has also been concluded that, in well-perfused tissues *in vivo* other than the central nervous system, the free cholesterol content would exchange completely with circulating free cholesterol within about 1 day.<sup>15</sup> Not surprisingly, therefore, lowering of circulating cholesterol levels in hypercholesterolaemic patients by treatment with pravastatin has been shown to result in decreases in erythrocyte and platelet membrane cholesterol contents.<sup>16</sup> Moreover, these changes were associated with an increase in Na<sup>+</sup> pump activity in these membranes. Although the wider implications of these observations for the functioning of other cell types were pointed out by the authors, there appear to be no related reports in the literature to date.

With regard to the central nervous system, whole brain levels of cholesterol are found to be quite stable. The turnover is very low, the source of new cholesterol being synthesis in the brain rather than circulating plasma cholesterol, for which a blood/brain barrier may operate.<sup>17,18</sup> Myelin contains a substantial proportion of the brain cholesterol and may account for the stable level overall. It is possible, however, that the fraction of cholesterol present in grey matter may be more labile. For example, mice fed a diet containing 5% cholesterol for 8 weeks, which resulted in a 200% increase in serum cholesterol, were found to have no significant increase in whole brain cholesterol but they did show a significant 20% increase in cholesterol measured in frontal cortex, which has less white matter than the brain as a whole.<sup>19</sup> Increases in brain cholesterol as a result of

atherogenic diets have also been reported for rabbits, in which the regional increases were correlated with increases in  $\beta$ -amyloid immunoreactivity,<sup>19</sup> and for rats, in which there was an associated fall in brain Ca<sup>2+</sup>-ATPase activity.<sup>21</sup>

A more subtle effect has been seen in mice on a chronic ethanol diet. Although there was no consistent change in brain cholesterol content, there was a significant shift in the asymmetric distribution of cholesterol between cytofacial and exofacial leaflets of synaptic plasma membranes. In control mice, 88% of the membrane cholesterol was present in the cytofacial leaflet whereas in the ethanol-treated mice this was reduced to 72%.<sup>22</sup> A corresponding increase in fluidity of the cytofacial leaflet and decrease in fluidity of the exofacial leaflet was found in the ethanol-treated compared with the control mice.<sup>23</sup> A similar redistribution of synaptic plasma membrane cholesterol has been seen with ageing in mice.<sup>24</sup>

### CHOLESTEROL AND NEURODEGENERATION

In Alzheimer's disease (AD), an association with cholesterol is recognised, although poorly understood and often overlooked.<sup>25</sup> A study on membranes prepared from cortical grey matter of AD patients showed that the cholesterol/phospholipid molar ratio was reduced by 30% in the temporal gyrus but unaffected in the cerebellum, which correlated with a reduced width of the bilayer and changes in electron density selectively in the temporal gyrus.<sup>26</sup> This aberrant pattern could be restored to that found in the membranes from non-AD controls by cholesterol enrichment of the AD membranes. Additionally, in hippocampus and frontal cortex of AD patients, it has been shown that apolipoprotein E levels are decreased compared with the levels in non-AD tissue.<sup>27</sup> It is of interest, therefore, that apoE-knockout mice show many of the neurotransmitter deficits and loss of memory that are characteristic of AD<sup>28,29</sup> and also show a reduced cholesterol content in synaptic plasma membranes with a preferential reduction in the cytofacial leaflet.<sup>30</sup> Correspondingly, there is evidence that induced depletions of neuronal cholesterol can affect synaptic plasticity and neurodegeneration.<sup>31</sup>

### PROSPECT

Many of the studies cited above are the work of individual research groups. There is a need for consolidation of the information base by confirmation of key observations in different

laboratories as well as further exploration of possible functional effects of membrane cholesterol. This is an area of research that deserves more attention.

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