# Good essay about lipid bilayers: synthesis of cholesterol and the role of circadi...

Science, Genetics

# “ Abstract”

Cholesterol plays a pivotal role in the fluidity of plasma membrane in cells. Evidence of cholesterol evolution from lanosterol suggests that cholesterol has little sensitivity to changes in temperature as opposed to lanosterol. Simulations also revealed that there is no ld-lo coexistence and 3-phase lines in lipid/lanosterol systems as opposed to lipid/cholesterol systems. The sterol also favors a strong interaction with lipids having saturated acyl chains (Miao et al.) which is a key factor in understanding and characterizing the lipid bilayer model. Based on surface potential measurements, cholesterol and ergosterol reduce the penetration of water into the lipid monolayer. Results revealed that excess free energy of mixing stabilizes binary monolayers containing cholesterol as compared to those with ergosterol or lanosterol. Some studies also demonstrated that circadian rhythm influences cholesterol synthesis (Acimovic et al.). Succeeding studies of Acimovic et al. showed that the lack in CREM isoforms bypassed Cyp51 gene during the regulated de novo cholesterol synthesis.

1. From Lanosterol to Cholesterol: Molecular and Thermodynamics Behavior

The concentration of cholesterol is essential in the fluid function of the plasma membrane in the mammalian cells. It has been argued that lanosterol is the precursor in the molecular evolution of cholesterol (Bloch as cited by Miao et al., 1429-1444). Several studies have been undertaken to elucidate the synthesis of cholesterol. Miao et al. (1429-1444) attempted to build a classification system of reference with respect to the thermodynamics behavior of lanosterol-lipid and cholesterol-lipid membranes via phase-equilibria. They also aim to gain more insights on the

fundamental molecules involved within the phase equilibria. Conformational ordering of lipid molecules and thermal behavior of bilayer membranes were characterized. Models were used to understand the interactions and molecular processes involved in lanosterol evolution to cholesterol. For solid-state deuterium-NMR spectroscopy analysis, they obtained 1-palmitoyl-2-petroselinoyl-sn-glycerol-3-phosphatidylcholine (PPetPC) then perdeuterated the lipid to form PPetPC-d31. Sampling methods were modified to address the difficulty in linking barrier crossing to first-order phase transitions (Nielsen et al. cited in Miao et al. 1429-1444). It has been noted that lack of sterol PPetPC displays a single endothermic peak. However, peak temperature drops when adding sterol groups. There is also a coexistence of lo (liquidus) and so (solidus) phase. PPetPC/cholesterol system has a vertical solidus boundary at temperatures ranging from 0-12°C. The PPetPC/lanosterol system revealed a solidus liquidus lines moving towards higher lanosterol mole fractions. This suggested that cholesterol has little sensitivity to changes in temperature as opposed to lanosterol. Simulations also revealed that there is no ld-lo coexistence and 3-phase lines in lipid/lanosterol systems compared to the other system. Both systems exhibit a critical point but cholesterol has a more stable critical point. Consistent to experimental results, simulations revealed that cholesterol and its precursor lanosterol have order inducing effects on lipid chains—cholesterol has a stronger effect. The lo structure found in the lipid-cholesterol bilayer membranes may resolve the conflicting aspects of the cell membrane. Cholesterol strongly favors interacting with lipids having saturated acyl chains and its concentration is higher in the lo domains than in ld domains.

Thus, the evolution of lanosterol to cholesterol shows the capacity of sterols to stabilize a liquid-ordered phase and induce a collective order in the acyl chain conformations.

Sabatini, Mattila and Kinnunen (2340-2355) analyzed binary mixtures of cholesterol, ergosterol, and lanosterol with phosphatidylcholines at different lengths of saturated acyl chains DPPC and DMPC. They used Langmuir balance to determine how sterols modify the biophysical properties of membranes. They found that there was a transition of mixed monolayers with DPPC from expanded to condensed liquid after increasing the concentrations of ergosterol, lanosterol and cholesterol. Cholesterol and ergosterol affects the absence of inflection in phase behavior of fluid DMPC. There was a pronounced discontinuity between mole fractions of lanosterol—X¼ 0. 3 and X ¼ 0. 75—during compression of isotherms. Varying Xsterols and monolayer physical states affect condensation and expansion of liquid in force area isotherms. Surface potential measurements revealed that cholesterol and ergosterol reduce the penetration of water into the lipid monolayer. Excess free energy of mixing stabilizes binary monolayers containing cholesterol compared to those with ergosterol or lanosterol. The range of surface pressure values found in natural membranes explains the differences in those three sterols.

Using a model, Putzel and Schick (869-877) attempted to describe the thermodynamic behavior of a lipid bilayer in the cell membrane in two coupled leaves. They considered two cases. First, both inner and outer leaves will undergo phase separation when uncoupled from one another. Second, the outer layer can undergo different phase separation by itself

while coupled to the inner leaf that cannot. The bilayer can exist in four phases and can exhibit three-phase coexistence. Data indicated that bilayer is only able to exist in two phases when coupling is weak. The outer layer abounds in ordering lipids while the inner leaf is richer when uncoupled. Outer layer lacks ordering lipids while the inner leaf lacks more ordering lipids during uncoupling. Differences in densities of ordered lipids in the inner leaf may help distinguish boundaries of inner leaf. Large osmotic compressibility is also critical to the composition of both the inner and outer leaf. Increased coupling increases the effect on the inner leaf because of slight changes in the outer leaf. Thus, sufficient large coupling allows a phase transition and four phases to occur in the bilayer. The alignment of domains in one leaf suggests that uncoupled domains would be uncorrelated when leaf undergoes phase separation even when uncoupled from the other and vice versa.

2. The Role of Circadian Rhythm

Prior to revealing the relationship of cholesterol synthesis to circadian rhythm, Acimovic et al. (206-210) demonstrated how isoforms of Crem regulate circadian expression of Cyp51 and other cholesterogenic genes in mouse liver. The study shows that expression of Cyp51, Hmgs, Fpps, and Sqs is minimal in CT12 and CT16 and peaks between CT20 and CT24 in wild type mice. For mice having Crem negative/negative livers, Cyp51, Fpps, and Sqs lost circadian behavior while Hmgcr is phase advanced from CT20 to CT12. The results agree to phase advance ratio of lathosterol/cholesterol as detected by GC–MS. When Crem genes overexpressed transcription factors CREMs and ICER, Hmgcr proximal promoter were not affected while

transcription factors influence expression from the CYP51 promoter. This indicates that Crem-dependent regulation of Cyp51 in the liver results in circadian expression of this gene. The authors inferred that cAMP signaling may affect the circadian regulation of cholesterol synthesis on the periphery.

The relationship of cholesterol synthesis and circadian rhythm was further elaborated in the study of Acimovic et al. (635-641) on the intermediates in cholesterol synthesis vis-à-vis circadian rhythm. They compared Crem-knock-out mice and wild type of mice to determine how “ cAMP response element modulator” (CREM) isoforms influence cholesterol synthesis through time. They used multiple linear regression and cosinor and modeled a 24 hour profiles across genotypes, gender and zeitgeber time for the following sterols: lanosterol; 24, 25-dihydrolanosterol (DHL); testis meiosis-activating sterol (TMAs); 7-dehydrocholesterol (DHC); and cholesterol. Transcription factors CREM and ICER from Crem genes bind to cAMP-responsive elements promoters which control the expression of CRE-containing genes. A post-squalene cholesterogenenic enzyme CYP51 converts lanosterol to follicular fluid meiosis-activating sterol (FF-MAS) and DHL to 24, 25-dihydro-FF-MAS. The lack of CREM isoforms shows that male mice of both genotypes had the maximal ratio between free lathosterol and total cholesterol in the liver during the dark phase. While lanosterol and T-MAS oscillated in synchrony as the phase values becomes similar for the ZT (range 15. 2 – 17. 7 hours), the phase for 7-DHC shifted by approximately 2 hours, into the dark phase. Results seem to coincide with the cholesterol reaction pathway where lanosterol and TMAS are cholesterol synthesis precursors, while 7-DHC is a

metabolite before the final product cholesterol. The concentrations of these sterols were higher in female mice than that of the males. The genotype/gender factors have no effects on the circadian circulation of these sterols except for 24, 25-dihydrolanosterol. The absence of CREM isoforms bypassed Cyp51 gene during the regulated de novo cholesterol synthesis. Thus, changes in the 24-h time-dependent profile of the expressed Cyp51 gene do not significantly affect the circadian rhythm of the sterol intermediate in the pathway. Peak in cholesterol synthesis relates to the nocturnal feeding cycle of mice which may be the main stimulus for cholesterol synthesis clock in the liver.

Figure 1 shows the cholesterol synthesis pathway in the cell (Liscum, 411). Figure 2 illustrates a detailed pathway for the final synthesis of cholesterol from lanosterol (Liscum, 410).

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