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Review Article

Statins and their influence on brain cholesterol

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24S-Hydroxycholesterol;
Lathosterol;
Statins

BACKGROUND: Growing evidence suggests that different statins are able to lower brain cholesterol synthesis. It is not clear yet whether lipophilic statins influence brain cholesterol in different way than hydrophilic ones.

SOURCES OF MATERIAL: The MEDLINE database.

FINDINGS: According to the data reported thus far, statins may influence brain cholesterol metabolism directly (because they are able to penetrate BBB no matter whether they are hydrophilic or lipophilic) and also indirectly (by lowering plasma cholesterol). Although the definite mechanism is not known yet, it becomes obvious that statins do not only influence peripheral but also central cholesterol pool.

CONCLUSION: Better understanding of the effects of statins on brain metabolism becomes more important because many studies bring evidence of a possible link between cholesterol and neurodegeneration.

Association between Alzheimer disease (AD) and cholesterol

Neurons, like all other cells in the body, must have a continuous supply of unesterified cholesterol, and this sterol must come either from de novo synthesis within the nerve cells or from the uptake of cholesterol from the extracellular environment. Changes in net cholesterol balance across the whole body may alter sterol balance across the central nervous system and also contribute the development of neurodegeneration. AD is a neurodegenerative disorder with progressive cognitive impairment, personality changes, and memory deficits largely attributable to deficiency in cholinergic neurotransmission. Histopathologically, the unit is characterized by an abnormal brain accumulation of amyloid β-peptide (Aβ). The relationship between Aβ and cholesterol has been studied during the past few years, and a number of epidemiologic studies suggest an association between plasma cholesterol and risk for AD. Greater serum levels of cholesterol elevate Aβ and facilitate its deposition into plaques, which is of importance for the development of AD.[1] These findings raise the question of whether cholesterol-lowering drugs influence brain cholesterol metabolism and consequently amyloidogenesis, which has been proved in several recent studies on animals.[2,3] The most widely prescribed cholesterol-lowering drugs, statins, are inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which controls the first step in the biosynthesis of cholesterol.

The authors of several studies have recently demonstrated a beneficial effect of statins on the brains of patients with AD: statins decreased oxidative stress, glial activation, and the number of Aβ plaque-associated dystrophic neurites in the cerebellum; they up-regulated endothelial nitric oxidase synthase expression; and they maintained the number of Purkinje cells and their synaptic networks in the AD cerebellum.[4]

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Methods for evaluation of cholesterol metabolism

To study brain cholesterol metabolism, lathosterol and oxysterols as 24S-hydroxycholesterol and 27-hydroxycholesterol are used. Lathosterol is a cholesterol precursor and a marker for cholesterol endogenous synthesis. To measure the absolute rate of sterol synthesis in vivo, the quantitation of the rates of incorporation of either 2H or 3H atom from [2H] water or [3H] water into the cholesterol molecule is recommended.[5] In contrast to their parent molecule cholesterol, two of its side-chain oxidized metabolites are able to cross the blood−brain barrier (BBB). Cholesterol 24-hydroxylase in the brain is capable of converting cholesterol to 24S-hydroxycholesterol (cerebrosterol), which crosses the BBB, enters plasma, and hence can be used as a marker for cholesterol elimination.[5] There is also an opposite flux of 27-hydroxycholesterol over the BBB, which is formed to a lower extent in the brain than in most other organs and is also taken up by the liver.[6,7] The distribution of this oxysterol in human brain was found to be consistent with an extracerebral origin, with a concentration gradient from the white to the gray matter, a situation opposite that of 24S-hydroxycholesterol, which is exclusively formed in brain.[6] The flux of 27-hydroxycholesterol from the circulation into the brain may regulate a number of key enzymes within the brain and represents the missing link between AD and hypercholesterolemia.[8]

Impact of statins on total brain cholesterol

Both experimental and clinical trials have investigated the effects of different statins on biomarkers of cholesterol synthesis and elimination. The results of these studies are summarized in Tables 1 and 2. Comparing the results of aforementioned studies has several limitations, eg, the levels of used statins and the duration of treatment differ; the levels of statins used in experimental studies are many times greater than the common dose in humans.

In general, the data are inconsistent concerning the impact of statins on total brain cholesterol[9–11] (measured in brain homogenate in animals or in cerebrospinal fluid [CSF] in humans).

Effect of statins on cholesterol synthesis in brain

However, the results of the studies are quite consistent concerning the efficiency of statins to suppress brain cholesterol synthesis both in animals and humans, which

Table 1 Summary of statin effects on biomarkers for cholesterol metabolism: experimental studies

	Statin, dosage	Duration of the study	Type of animal	Levels in plasma	Levels in brain
Eckert, 2001[9]	Lovastatin 100 mg/kg/day	23 days	Normal mice	ø Cholesterol	↓ Cholesterol
			ApoE-deficient mice	ø Cholesterol	ø Cholesterol
Pentaceska, 2002[11]	Atorvastatin 30 mg/kg/day	8 weeks	Transgenic PSAPP mice	↓ Cholesterol	ø Cholesterol (in cortex)
Johnson-Anuna, 2005[29]	Lovastatin 100 mg/kg/day	21 days	Normal mice		ø Cholesterol
	Pravastatin 100 mg/kg/day				↓ Cholesterol
	Simvastatin 50 mg/kg/day				↓ Cholesterol
Lutjohann, 2004[15]	Pravastatin 300 mg/day	3 weeks	Guinea pigs	↓ Cholesterol	ø Cholesterol
				↓ Lathosterol/ cholesterol	↓ Lathosterol
					↓ 24S-OH-chol
					↓ Lathosterol/ cholesterol
	Simvastatin 150 mg/day			↓ Cholesterol	ø Cholesterol
				↓ Lathosterol/ cholesterol	↓ Lathosterol
					ø 24S-OH-chol
					↓ lathosterol/ cholesterol
Thelen, 2006b[21]	Pravastatin 200 mg/kg/day	3 days	Normal mice	ø Cholesterol	ø cholesterol
				↓ Lathosterol	ø lathosterol
				ø 24S-OH-chol	ø 24S-OH-chol
	Simvastatin 100 mg/kg/day			ø Cholesterol	ø cholesterol
				↓ Lathosterol	↓ lathosterol
				ø 24S-OH-chol	ø 24S-OH-chol
Franke, 2007[10]	Simvastatin 50 mg/kg/day	21 days	Guinea pigs	↓ Cholesterol	ø Cholesterol

ApoE, apolipoprotein E; Ø, no change.