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Perspective

Cholesterol-independent neuroprotective and neurotoxic activities of statins: Perspectives for statin use in Alzheimer disease and other age-related neurodegenerative disorders☆

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ABSTRACT

Statins, long known to be beneficial in conditions where dyslipidemia occurs by lowering serum cholesterol levels, also have been proposed for use in neurodegenerative conditions, including Alzheimer disease. However, it is not clear that the purported effectiveness of statins in neurodegenerative disorders is directly related to cholesterol-lowering effects of these agents; rather, the pleiotropic functions of statins likely play critical roles.

Moreover, it is becoming more apparent with additional studies that statins can have deleterious effects in preclinical studies and lack effectiveness in various recent clinical trials.

This perspective paper outlines pros and cons of the use of statins in neurodegenerative disorders, with particular emphasis on Alzheimer disease.

1. Basic pharmacology of statins

Statins are a family of drugs with pleiotropic functions. To this class belong 8 drugs: mevastatin and lovastatin, which were the first developed and studied in humans; pravastatin and simvastatin, which can be considered as derivatives of the parental lovastatin; and atorvastatin, fluvastatin, rosuvastatin and pitavastatin, which are distinct synthetic compounds [1]. Due to their main mechanism of action, namely the inhibition of the hydroxylmethyl-glutaryl-CoA (HMG-CoA) reductase, statins are widely used for the treatment of dyslipidemias [1]. By inhibiting HMG-CoA reductase, statins block the conversion of HMG-CoA into mevalonate, the first step in cholesterol biosynthesis [1,2]. As a result of statin administration, low-density lipoprotein (LDL)-cholesterol synthesis decreases in hepatocytes and this reflects a reduced cholesterol blood level. In addition to this effect, statins have been shown to reduce triglyceride and increase HDL-cholesterol plasma levels. Taken together, the composite effect of statins in reducing triglycerides and LDL-cholesterol, coupled with the increase in HDL-cholesterol, put these drugs in the arena of cardiovascular agents, due to their ability to counteract hyperlipidemias, the major cause of atherosclerosis which, in turn, is a common pathogenetic mechanism for coronary artery disease, ischemic cerebrovascular disease and peripheral vascular disease [1,2].

Although statins share the same main mechanism of action, their pharmacokinetic profile is quite different (Table 1). All statins are well absorbed by the intestine when given by orally, even though they undergo marked first-pass effects by the liver, which reduces the systemic biovailability (5–30%) [1]. With the exception of simvastatin and lovastatim, which are pro-drugs and require hepatic activation, other statins are administered as β-hydroxy-acids. Upon administration, statins reach peak plasma concentration, ranging from 10 to 448 ng/ml, within 0.5–4 h. In the plasma, statins are bound to albumin (43–99%) and this binding accounts for their variable half-life [1]. Atorvastatin and rosuvastatin are the statins with the longest half-life (15–30 and 20.8 h, respectively), whereas fluvastatin, lovastatin, pravastatin and simvastatin have half-lives around 0.5–3 h [1]. All statins are metabolized by the liver through the isoforms 3A4 (atorvastatin, lovastatin and simvastatin) and 2C9 (fluvastatin and rosuvastatin) of the cytochrome-P-450 (CYP) system, whereas pravastatin undergoes sulfation. The primary route of elimination is fecal, and only a minor fraction of statins is eliminated via urine [1,2].

The main adverse effects of statins are hepatotoxicity and myopathy. A transient elevation of serum transaminases (up to 3-times the baseline value) is a common outcome of statin therapy

☆ Perspective articles contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

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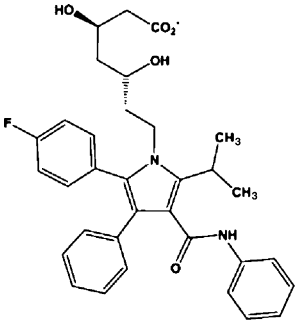
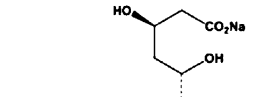
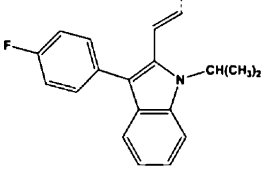
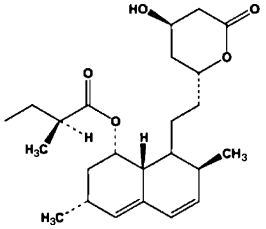
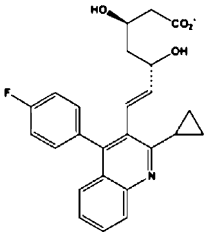
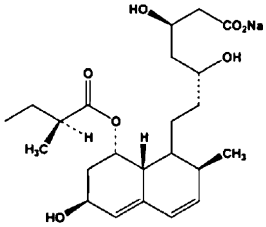
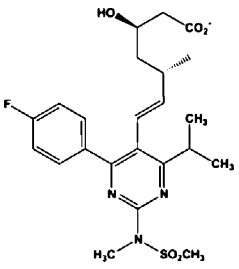
Table 1
Pharmacokinetic parameters of statins.

		T_{max} (h)	C_{max} (ng/ml)	B (%)	L	Pb (%)	M	$T_{1/2}$ (h)	E (%)
Atorvastatin		2–3	27–66	12	Yes	80–90	CYP3A4	15–30	Urinary 2 Fecal 70
Fluvastatin		0.5–1	448	19–29	Yes	>99	CYP2C9	0.5–2.3	Urinary 6 Fecal 90
Fluvastatin XL		4	55	6	Yes	>99	CYP2C9	4.7	Urinary 6 Fecal 90
Lovastatin		2–4	10–20	5	Yes	>95	CYP3A4	2.9	Urinary 10 Fecal 83
Pitavastatin		1.2	41	~80	Yes	96	CYP2C9	11	Urinary <2 Fecal 90
Pravastatin		0.9–1.6	45–55	18	No	43–55	Sulfation	1.3–2.8	Urinary 20 Fecal 71
Rosuvastatin		3	37	20	No	88	CYP2C9	20.8	Urinary 10 Fecal 90