Direct free radical scavenging effects of water-soluble HMG-CoA reductase inhibitors

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3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, statins, are widely used for preventing cardiovascular and cerebrovascular diseases by controlling blood cholesterol level. Additionally, previous studies revealed the scavenging effects of statins on free radicals. We assessed direct scavenging activities of two water-soluble statins, fluvastatin and pravastatin, on multiple free radicals using electron spin resonance spectrometry with spin trapping method. We estimated reaction rate constants (k_{fv}, for fluvastatin, and k_{pv}, for pravastatin). Superoxide anion was scavenged by fluvastatin and pravastatin with k_{fv} and k_{pv} of 4.82 $M^{-1}s^{-1}$ and 49.0 $M^{-1}s^{-1}$, respectively. Scavenging effects of fluvastatin and pravastatin on hydroxyl radical were comparable; both k_{fv} and k_{pv} were >10^9 $M^{-1}s^{-1}$. Fluvastatin also eliminated *tert*-butyl peroxyl radical with relative k_{fv} of 2.63 to that of CYPMPO, whereas pravastatin did not affect *tert*-butyl peroxyl radical. Nitric oxide was scavenged by fluvastatin and pravastatin with k_{fv} and k_{pv} of 68.6 $M^{-1}s^{-1}$ and 701 $M^{-1}s^{-1}$, respectively. Both fluvastatin and pravastatin had scavenging effects on superoxide anion, hydroxyl radical and nitric oxide radical. On the other hand, *tert*-butyl peroxyl radical was scavenged only by fluvastatin, suggesting that fluvastatin might have more potential effect than pravastatin to prevent atherosclerosis and ischemia/reperfusion injury via inhibiting oxidation of lipids.

Key Words: **water-soluble statin, electron spin resonance spectrometry, free radical, fluvastatin, pravastatin**

Excessive accumulation of reactive oxygen species or free radicals increases the risk for various cardiovascular and cerebrovascular diseases.[1,2] One of the major mechanisms of such pathology is atherosclerosis. Recent basic researches demonstrated that oxidized low-density-lipoprotein accelerated the formation of atherosclerosis.[3] It was shown that metabolic abnormalities of lipids such as cholesterol and free fatty acid (FFA) correlated with the prognosis of whole body ischemia/reperfusion (I/R).[4,5] These findings suggested that lipid oxidation is closely involved in various pathological conditions. Research and development of drugs to prevent the production of free radicals or oxidation of lipids have been conducted in recent years. Edaravone is the only radical scavenger that has been used in clinical practice.[6] Although it had been confirmed that edaravone could exert anti-oxidative effect via oxidation of itself *in vitro*,[7] the clinical usefulness of other radical scavengers has not been established yet.

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, statins, are now widely used for the prevention of cardiovascular or cerebrovascular diseases via lowering serum cholesterol level. It is also known that statins have anti-oxidative effect, which encourages the usage of statins to prevent cerebrovascular and cardiovascular diseases. In fact, several clinical researches revealed such additional benefits of statins to improve patients' outcome.[8,9] Moreover, several basic researches also showed that statins could reduce hydroxyl radical *in vitro*, or prevent cholesterol-induced oxidative stress in laboratory animals.[10-12] Fluvastatin is a compound with a fluorophenyl indole ring and an enoic acid, and pravastatin is a compound with a naphthalene frame and an enanthate (Fig. 1). Fluvastatin has double bonds in enoic acid conjugated with an indole ring that has shown to have radical scavenging activity,[13] and the same structure is not involved in pravastatin. Therefore, it appears that fluvastatin could have stronger radical scavenging activity than pravastatin.

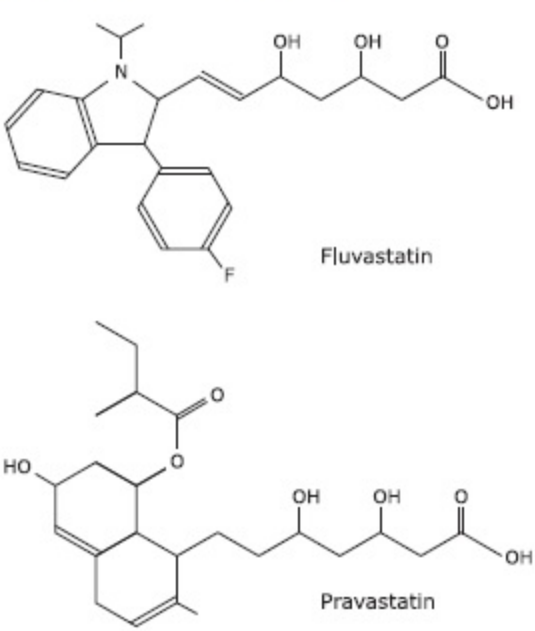

Fig. 1. Structure of water-soluble statins, fluvastatin (A) and pravastatin (B).

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