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Oral vitamin-A-coupled valsartan nanomedicine: High hepatic stellate cell receptors accessibility and prolonged enterohepatic residence

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Abstract:

So far, liver fibrosis still has no clinically-approved treatment. The loss of stored vitamin-A (V_A) in hepatic stellate cells (HSCs), the main regulators to hepatic fibrosis, can be applied as a mechanism for their targeting. Valsartan is a good candidate for this approach; it is a marketed oral-therapy with inverse- and partial-agonistic activity to the over-expressed angiotensin-II type1 receptor (AT1R) and depleted nuclear peroxisome proliferator-activated receptor-gamma (PPAR-γ), respectively, in activated HSCs. However, efficacy on AT1R and PPAR-γ necessitates high drug permeability which is lacking in valsartan. In the current study, liposomes were used as nanocarriers for valsartan to improve its permeability and hence efficacy. They were coupled to V_A and characterized for HSCs-targeting. Tracing of orally-administered fluorescently-labeled V_A-coupled liposomes in normal rats and their fluorescence intensity quantification in different organs convincingly demonstrated their intestinal entrapment. On the other hands, their administration to rats with induced fibrosis revealed preferential hepatic, and less intestinal, accumulation which lasted up to six days. This indicated their uptake by intestinal stellate cells that acted as a depot for their release over time. Confocal microscopical examination of immunofluorescently-stained HSCs in liver sections, with considerable formula accumulation, confirmed HSCs-targeting and nuclear uptake. Consequently, V_A-coupled valsartan-loaded liposomes (VLC)-therapy resulted in profound re-expression of hepatic Mas-receptor and PPAR-γ, potent reduction of fibrogenic mediators' level and nearly normal liver function tests. Therefore, VLC epitomizes a promising antifibrotic therapy with exceptional extended action and additional PPAR-γ agonistic activity.

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