Figure 1: In a healthy state, toxins are processed and removed from the cells and organs via enzymes and transporter proteins, and leave the body primarily via the skin, urine, and feces.

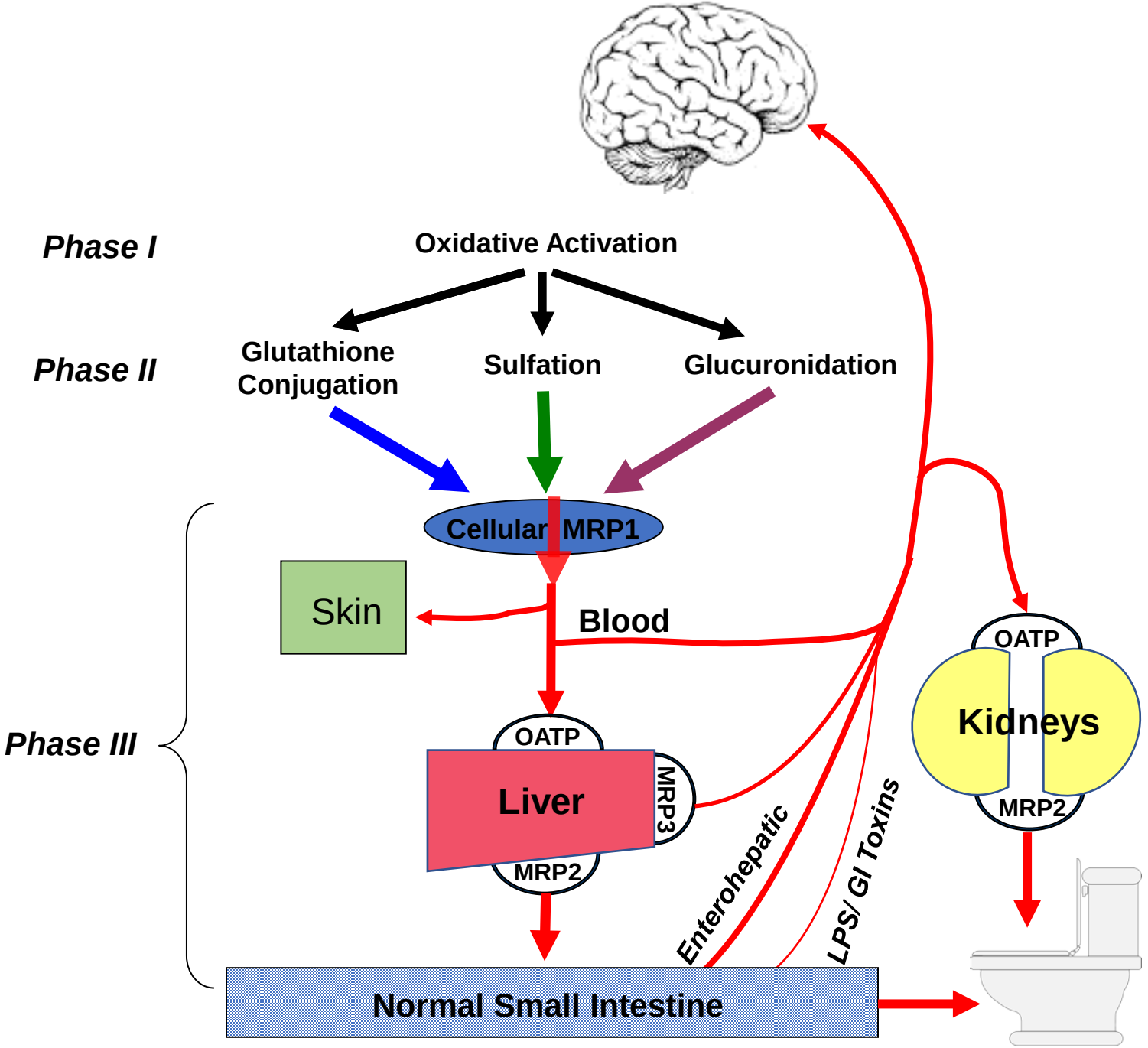


Figure 2: Oxidative stress causes Nrf2 to dissociate from binding protein (Keap1) in the cytosol and translocate to the nucleus where it binds the promoter region (ARE), leading to transcription of detoxification enzymes and proteins. Various substances have been shown to have an inhibitory or inducing effect on the Nrf2/ARE pathway.

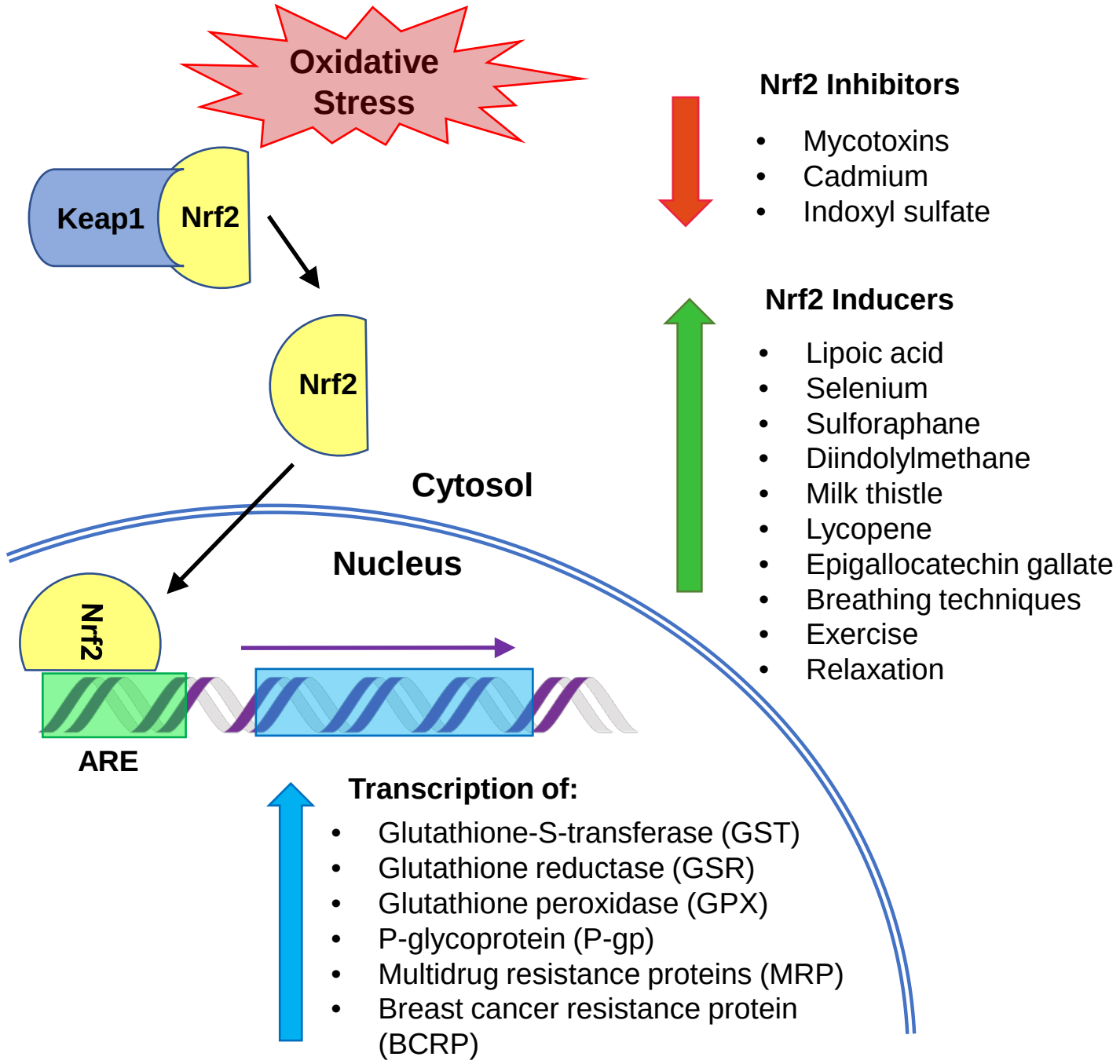
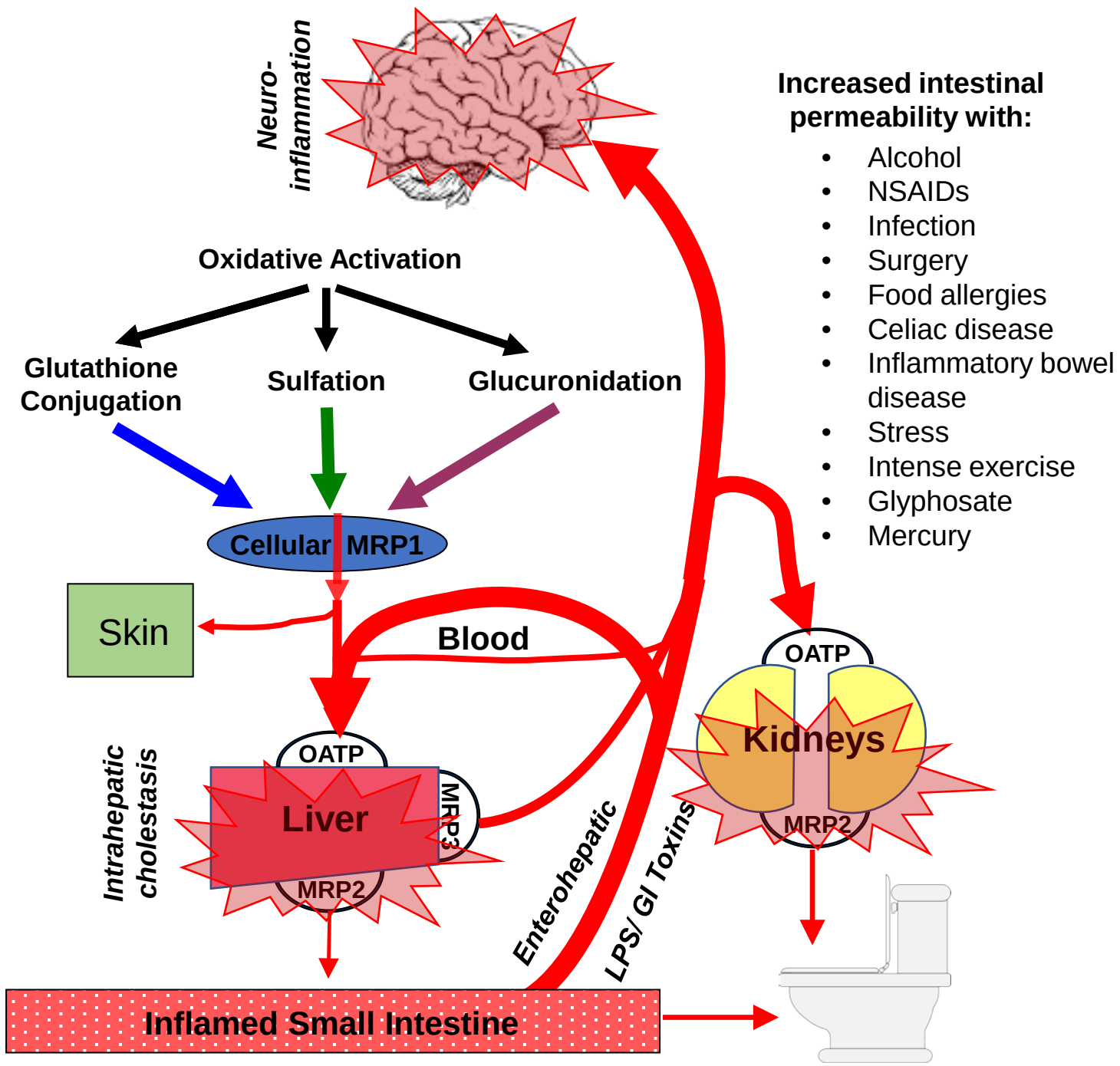


Figure 3: Gastrointestinal inflammation and increased intestinal permeability allow for endotoxin (LPS) to be released from bacteria in the gut into circulation. Endotoxin and related inflammatory cytokines block detoxification pathways by downregulating the detoxification enzymes and Phase III transporters, as well as contributing to cholestasis and kidney damage.



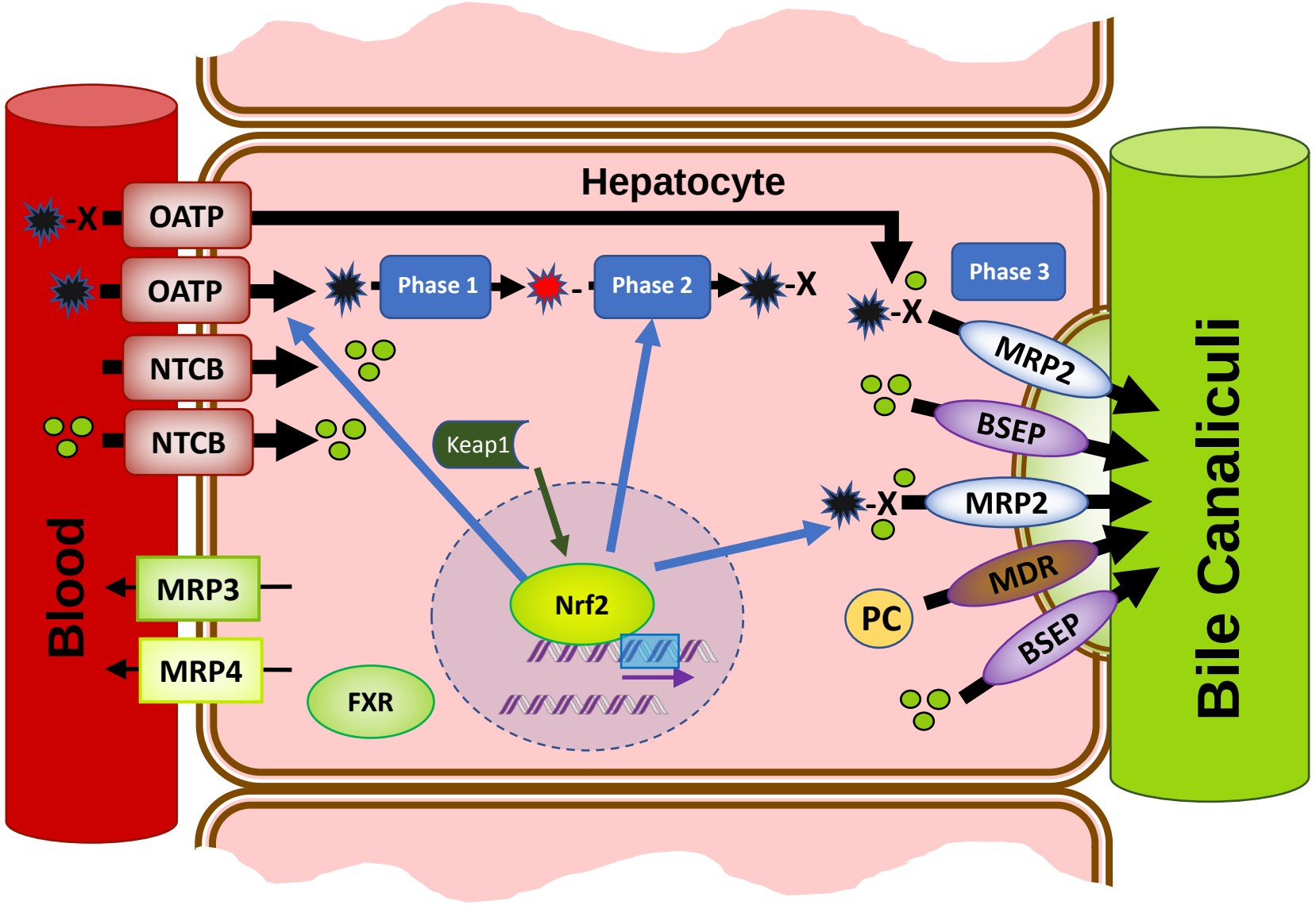


Figure 4a. Normal functioning hepatocyte. FXR remains in the cytosol until activated by bile acids. Oxidative stress causes Nrf2 to dissociate from Keap1 in the cytosol and bind ARE in the nucleus, increasing transcription of detoxification-related enzymes and proteins.

Bile Acids

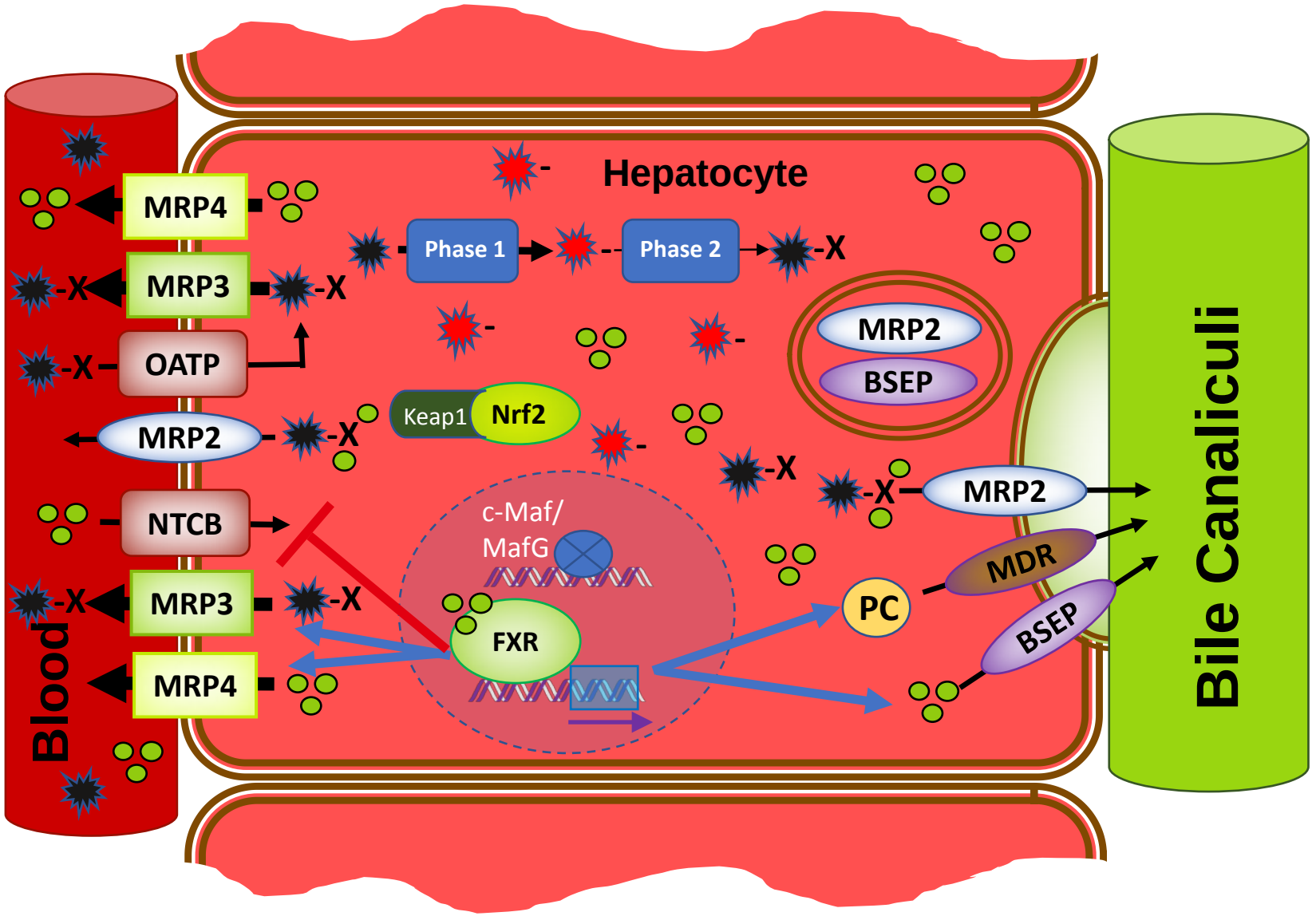
PC Phosphatidyl Choline

Toxins

- Phase 1 Activated Toxins

-X Toxin Conjugates

X = GSH, Sulfate, Glucuronate



Factors contributing to cholestasis:

- Estrogen
- Pregnancy
- Certain medications
- Endotoxin
- Inflammation
- Hepatic disease
- Biliary obstruction

Figure 4b: In cholestasis, there is reduced levels of BSEP and MRP2 at the canalicular membrane due to internalization and relocation. Binding of bile salts to FXR inhibits NTCB transport of bile acids into the cell and increases transcription of BSEP and MRP3 and 4 to lower intracellular bile acid concentration. Nrf2 is blocked from binding ARE by c-Maf/MafG, leading to reduced Phase II inactivation of toxins as well as diminished glutathione synthesis.

Note: this and the next 2 figures are the same data. Please use which one looks most clear on the print, and the color version if we pay for this.

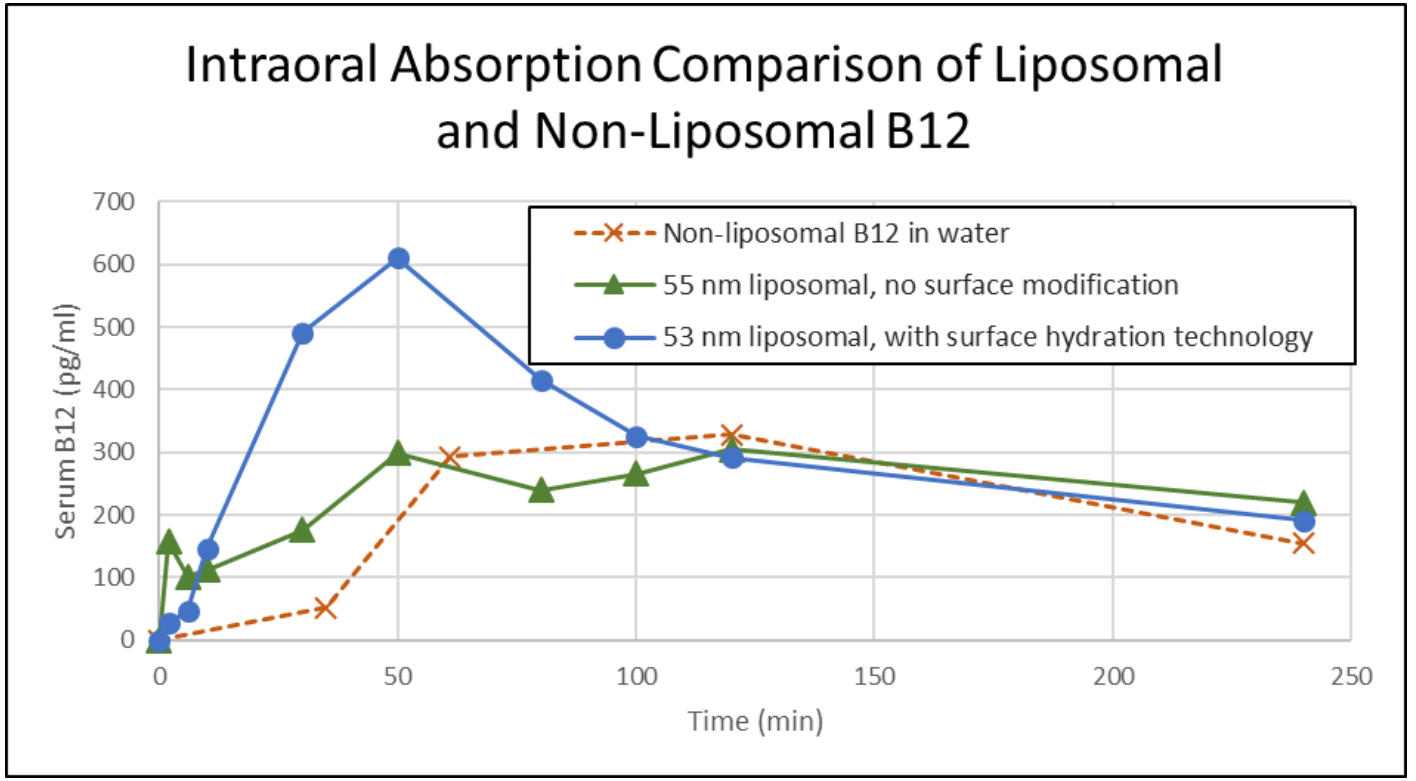


Figure 5 Comparison of B12 absorption intraorally in human subject.

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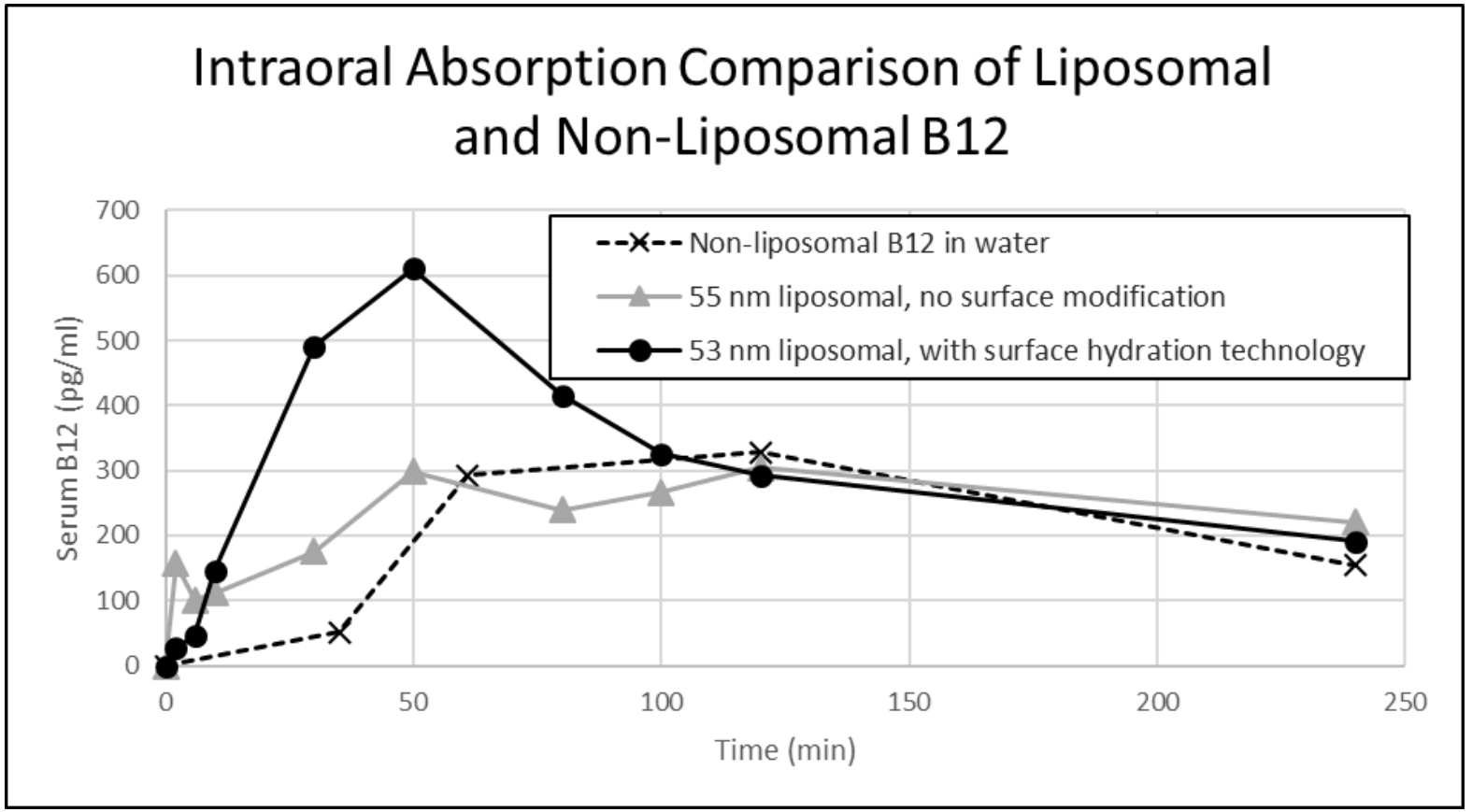

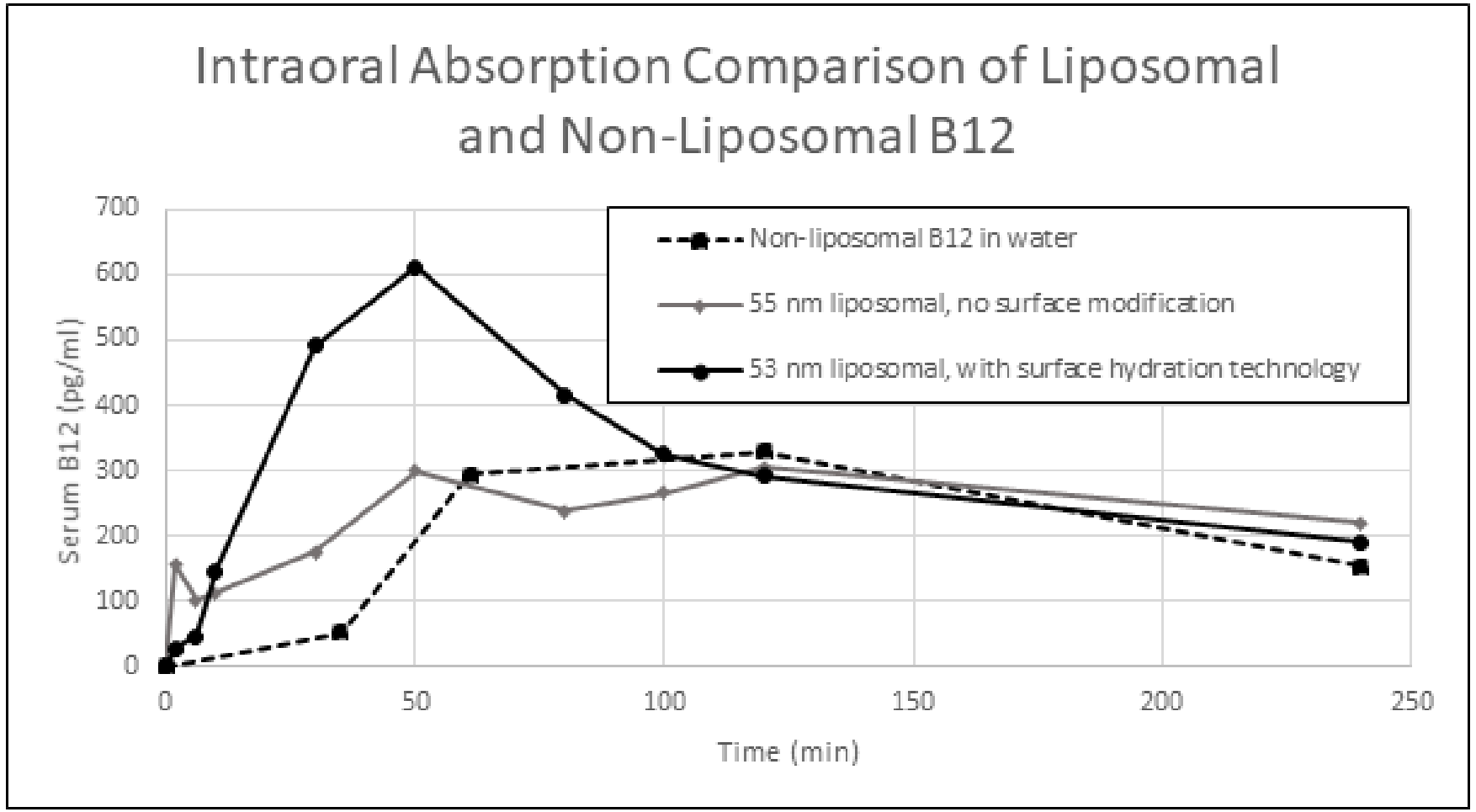

Figure 5 Comparison of B12 absorption intraorally in human subject.