3rd GLOBAL LIVER HEALTH FORUM

THE POTENTIAL MOLECULAR MECHANISM OF EPL: INSIGHTS FROM EASL 2022

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Introduction to EPL

The most abundant phospholipids that exist in mammalian tissues include PC and PE and are essential components in maintaining healthy cell membranes.[1] EPL are a hepatoprotective treatment that comprises a highly purified extract of PPC molecules from soybeans; the main active ingredient is DLPC, which corresponds to approximately 52% of the phospholipids in EPL.[2] NAFLD/MAFLD is the most common liver disease worldwide, and EPL have been shown to exert lipid-regulating properties, as well as multiple membrane protective effects.[2–4] While the therapeutic effects for such lipids have previously been described using clinical observations, fairly little is known about the molecular mechanisms of EPL.[2]

The *in-vitro* effect of EPL on pro-inflammatory cytokines

The effects of EPL and its constituents, PPC and PI on hepatocyte function were investigated in a recent study using steatosis cell lines *in vitro*.[5] EPL (0.1 and 0.25 mg/mL), PPC and PI (both at 0.1 and 1 mg/mL) in human hepatocyte cell lines (HepG2, HepaRG, steatotic HepaRG) versus untreated cells were assessed on the release of pro-inflammatory cytokines caused by treatment with LPS (a commonly studied glycolipid produced by most gram-negative bacteria) and lipid metabolising enzymes.[5]

In HepaRG cells treated with LPS, the addition of EPL (0.25 mg/mL; $p=0.0063$), PPC (1 mg/mL; $p<0.0001$) and PI (0.1 mg/mL; $p=0.0023$) significantly reduced the release of IL-6. However, in steatosis, LPS-treated HepaRG cell lines, treatment with EPL (0.1 mg/mL; $p<0.0001$) and PI (1 mg/mL; $p=0.0029$) led to an increase in the release of IL-6.[5] The reduction of IL-6 observed in the HepaRG cell lines supports the anti-inflammatory properties of EPL and its constituents, while the reduced activity in steatotic cells suggests a protective effect against the further development of steatosis.[5]

The *in-vitro* effect of EPL on lipid metabolising enzymes

There are many essential elements involved in lipogenesis.[6,7] For example, the enzyme G6PD is involved in the pathway that produces NADPH, which is required for fatty acid biosynthesis. Increased G6PD activity has previously been linked with fatty liver in rats.[7] G6PD activity remained unchanged with EPL, PPC and PI treatment in LPS-treated HepaRG and steatotic HepaRG cells.[5] Expression of rate-limiting enzymes such as acyl coenzyme A oxidase, which are higher in patients with NAFLD, have also shown to be reduced in LPS-treated HepaRG cell lines treated with EPL, PPC and PI.[5,8]

The build-up of fat in NAFLD is caused by an excess of the triglycerides and fatty acids that accumulate in the liver.[9] Fatty acid influx and synthesis within the liver can therefore lead to accumulation of fat deposits and steatosis. FAS, the enzyme that catalyses the final stage of fatty acid synthesis in the liver, may therefore have an association with steatosis.[9]

In LPS-treated HepaRG cells, FAS expression remained unchanged with EPL, PPC and PI treatment, whereas expression decreased with the same treatments in LPS-treated steatotic HepaRG cells.[5] Similarly, in rats with induced fatty liver, those receiving dietary PC showed no increase in FAS expression, whereas those without dietary PC did.[7] This suggests that PC administration in steatotic HepaRG cells may lead to a reduction in hepatically-produced fatty acids.[5]

References

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DLPC, 1,2-di-linoleoyl phosphatidylcholine; EPL, essential phospholipids; FAS, fatty acid synthase; G6PD, glucose-6-phosphate dehydrogenase; IL-6, interleukin-6; LPS, lipopolysaccharide; NADPH, nicotinamide adenine dinucleotide phosphate; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PPC, polyenylphosphatidylcholine.

Learning objectives:

- Introduce EPL as treatment for NAFLD/MAFLD
- Provide an overview of the first study of EPL in steatosis HepaRG cell lines and potential insights into the MoA of EPL
- Become familiar with the preclinical evidence supporting the MoA of EPL with respect to the effect on cytokines and lipid metabolising enzymes

Main takeaways:

- EPL can be used to treat liver diseases, including NAFLD/MAFLD, because of their hepatoprotective properties
- Several potential MoA of EPL have been elucidated from preclinical studies
- EPL, PPC, and PI have been shown to modulate activity and expression of liver metabolising enzymes *in vitro*
- As a result of these MoA, EPL may improve liver function and exert hepatoprotective effects

EPL, essential phospholipids; MoA, mechanism of action; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; PI, phosphatidylinositol; PPC, polyenylphosphatidylcholine.

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