INTRODUCTION

Intralipid is the brand name of an emulsion of fatty acids that has been used as a source of calories and essential fatty acids in parenteral nutrition for patients unable to consume nutrition orally. It is an emulsion of soybean oil, egg phospholipids, and glycerin, and it is available in 10%, 20%, and 30% concentrations. The major fatty acids in Intralipid are linoleic (44–62%), oleic (19–30%), palmitic (7–14%), linolenic (4–11%), and stearic (1.4–5.5%) acids. Weinberg’s group was the first to introduce Intralipid as an effective therapy to rescue bupivacaine toxicity in rat and canine models (1,2). They proposed the theory of the lipid sink and hypothesized that lipid emulsions form a lipid compartment entrapping bupivacaine (2,3). The Eghbali research group demonstrated multiple cardioprotective effects of Intralipid against ischemia-reperfusion injury (5-16). The exact mechanism of action of lipid emulsion has not yet been elucidated, but accumulating evidence suggests multimodal effects exist (4). Several recently discovered applications and effects of lipid emulsions are described below.

Direct Cardiac Effects of Intralipid

Inotropic Effect. Fettiplace et al. demonstrated the inotropic effects of lipid emulsion (17,18) by administering 20% soybean oil to male Sprague-Dawley rats and continuously measuring arterial pressure and aortic flow. Lipid infusion increased aortic flow and arterial pressure faster and to a greater extent than saline infusion. The infusion of lipid emulsion in isolated hearts increased the rate, pressure, and myocardial oxygen demand in a dose-dependent manner. Furthermore, the lipid infusion produced higher aortic flow and peak flows than saline infusion. This study showed that lipid emulsion in isolated hearts increased the rate, pressure, and myocardial oxygen demand in a dose-dependent manner. Furthermore, the lipid infusion produced higher aortic flow and peak flows than saline infusion. This study showed that lipid emulsion causes rapid, positive inotropic effects resulting in increased tissue blood flow that contributes to the phenomenon of the lipid rescue effect (18).
Calcium Influx. Gueret et al. evaluated the hemodynamic effect of Intralipid after verapamil intoxication and concluded that fatty acids increase Ca+ influx into cardiac myocytes, which motivates heart isotropy (19).

Fatty Acid Oxidation / Mitochondria / PI3K / Akt / ERK signaling. Studies done by Eghbali et al. investigate different aspects of Intralipid molecular mechanisms (11-16). They evaluated the hemodynamic function, infarct size, threshold for the opening of mitochondrial permeability transition pores, and phosphorylation levels of protein kinase B (Akt)/extracellular signal regulating kinase (ERK) in vivo rat hearts or isolated Langendorff-perfused mouse hearts that were subjected to ischemia followed by reperfusion with Intralipid (1% ex vivo and one bolus of 20% in vivo) or vehicle. They concluded that Intralipid inhibits the opening of mitochondrial permeability transition pores and protects the heart through glycogen synthase kinase-3β via PI3K/Akt/ERK pathways (13). In 2012, they compared the cardioprotective effects of Intralipid with cyclosporine-A, a potent inhibitor of mitochondrial permeability transition pore opening, both in vivo in rats and using the Langendorff technique. They concluded that although Intralipid inhibits the opening of the mitochondrial permeability transition pore as efficiently as cyclosporine-A, Intralipid is more effective in reducing the infarct size and improving the cardiac functional recovery (14). In another study, the same group pretreated rats with a single dose of a fatty acid oxidation inhibitor 5 min before inducing arrest with bupivacaine and then administered Intralipid. They observed high Ca+ retention capacity in cardiac mitochondria and improved cardiac function. They concluded that fatty acid oxidation is a requirement for the successful rescue of bupivacaine-induced cardiotoxicity by lipid emulsion, and they demonstrated this rescue effect via inhibition of mitochondrial permeability transition pore opening (15).

Opioid Receptors. In 2015, Partownavid and colleagues showed involvement of peripheral δ- and κ-opioid receptors in the rescue effect of lipid emulsion in bupivacaine-induced cardiotoxicity (16).

Ischemia-Reperfusion. In multiple experiments, the Eghbali group demonstrated that Intralipid mediated cardioprotective effects against ischemia reperfusion injury. In these experiments, Intralipid was able to reverse the heart damage, restore cardiac function, and limit the infarct size when compared with the control group (4-15). According to a recently published research study, lipid emulsion enhanced cardiac performance after ischemia-reperfusion in isolated squirrel hearts (20).

Leptin. In a recent study, Motayagheni et al. showed for the first time that crosstalk exists between Intralipid and leptin in cardioprotection. A leptin antagonist abolished Intralipid protection against ischemia-reperfusion injury in an ex vivo heart model (8).

Apoptosis/miRNA. Researchers investigating the effect of miRNA during the administration of Intralipid found that Intralipid was able to affect apoptosis via miRNA (6,11-12).

Receptors. In another study, Nadrowitz et al. indicated that lipid emulsion caused a reduction in the availability of NaV1.5, but both Intralipid and Lipofundin reversed NaV1.5 blocking by bupivacaine. These effects showed a direct interaction of lipids with NaV1.5, and also the ability of lipid emulsions to absorb bupivacaine with a consequent reduction of effective concentration (21). Umar et al. demonstrated the possible involvement of GPR40 in Intralipid protection (22).

Insulin Signaling. Fettiplace et al. demonstrated that glucose handling by AKT and AMPK is critical for rescue from bupivacaine cardiotoxicity. They showed that lipid emulsion enhances insulin signaling in bupivacaine-induced cardiotoxicity (23).

CONCLUSION

Recent Intralipid success stories have led to many trials investigating its mechanism of action in upstream and downstream pathways. Lipid emulsions may form a compartment as an oil droplet or simply remove the drugs in an action similar to that of soap micelles or cause loosening of the drug-receptor bond via a competitive effect. Furthermore, Intralipid may act as a “power source”
for an individual receptor or produce crosstalk with other agents such as leptin, and this may lead to the discovery of a new cascade and novel therapeutic targets. Despite the contradictory debates on mechanism of action, the volume of supporting evidence is enough to consider lipid emulsion as a novel protective target. In addition to understanding the underlying mechanism, further questions including appropriate dose, time of administration, and therapeutic window remain to be answered. Once we have answered these questions, we may be able to utilize lipid emulsion widely as a unique organ-protective agent.

REFERENCES

1. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. Toxicol Rev 2006;25:139-45.
2. Weinberg GL, VadeBoncouer T, Ramaraju GA, et al. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Anesthesiology 1998;88:1071-5.
3. Weinberg G, Lin B, Zheng S, et al. Partitioning effect in lipid resuscitation: further evidence for the lipid sink. Crit Care Med 2010;38:2268-9.
4. Motayagheni N (2016) From Bupivacaine to Intralipid: Leading Edge. J Anesth Crit Care Open Access 4(6): 00164. DOI: 10.15406/jacca.2016.04.00164
5. Li J, Ruffenach G, Kararigas G, et al. Intralipid protects the heart in late pregnancy against ischemia/reperfusion injury via Caveolin2/STAT3/GSK-3β pathway. J Mol Cell Cardiol 2017;102:108-16.
6. Li J, Motayagheni N, Barakati N, et al. Intralipid protects the heart in late pregnancy against ischemia/reperfusion injury by reducing cardiomyocyte apoptosis via Mir122 Induction. Circ Res 2016;119:A442.
7. Motayagheni N and Eghbali M. Complete reversal of xylazine-induced bradycardia with intralipid in female mice. Circ Res 2016;119:A253
8. Motayagheni N, Phan S, Eshraghi C, et al. Inhibition Of leptin receptor abolishes intralipid-induced cardioprotection against ischemia-reperfusion injury. Cardiology 2016;134:241.
9. Motayagheni N and Eghbali M. Reversal Of xylazine-induced bradycardia with intralipid. Cardiology 2016;134:431.
10. Motayagheni N. From Bupivacaine to intralipid: leading edge. J Anesth Crit Care 2016;4:00164.
11. Li J, Motayagheni N, Barakati N, et al. Intralipid protects the heart against ischemia/reperfusion injury by reducing cardiomyocyte apoptosis via miR122 induction in late pregnancy. Cardiology 2016;134:313.
12. Motayagheni N, Sharma S, Li J, et al. Implication of miR-1 and miR-144 in intralipid-induced cardioprotection against ischemia/reperfusion injury. Cardiology 2016;134:430.
13. Rahman S, Li J, Bopassa JC, et al. Phosphorylation of GSK-3β mediates intralipid-induced cardioprotection against ischemia/reperfusion injury. Anesthesiology. 2011;115:242-53.
14. Li J, Iorga A, Sharma S, et al. Intralipid, a clinically safe compound, protects the heart against ischemia-reperfusion injury more efficiently than cyclosporine-A. Anesthesiology. 2012;117:836-46.
15. Partownavid P, Umar S, Li J, et al. Fatty-acid oxidation and calcium homeostasis are involved in the rescue of bupivacaine-induced cardiotoxicity by lipid emulsion in rats. Crit Care Med. 2012;40:2431-7.
16. Partownavid P, Sharma S, Li J, et al. Involvement of opioid receptors in the lipid rescue of bupivacaine-induced cardiotoxicity. Anesth Analg. 2015;121:340-7.
17. Fettiplace MR, Pichurko A, Ripper R, et al. Cardiac depression induced by cocaine or cocaethylene is alleviated by lipid emulsion more effectively than by sulfobutylether-ß-cyclodextrin. Acad Emerg Med 2015;22:508-17.
18. Fettiplace MR, Ripper R, Lis K, et al. Rapid cardiotonic effects of lipid emulsion infusion. Crit Care Med 2013;41:e156-62.
19. Gueret G, Pennec JP, and Avrieux CC. Hemodynamic effects of intralipid after verapamil intoxication may be due to a direct effect of fatty acids on myocardial calcium channels. Acad Emerg Med 2007;14:761.
20. Salzman MM, Cheng Q, Declotz RJ, et al. Lipid emulsion enhances cardiac performance after ischemia-reperfusion in isolated hearts from summer-active arctic ground squirrels. J Comp Physiol B. 2017:10.1007/s00360-017-1071-z.
21. Nadorwitz F, Stoetzner C, Foadi N, et al. The distinct effects of lipid emulsions used for "lipid resuscitation" on gating and bupivacaine-induced inhibition of the cardiac sodium channel Nav1.5. Anesth Analg 2013;117:1101-8.
22. Umar S, Centala A, Barseghyan M, et al. Rescue of bupivacaine-induced cardiac arrest by lipid emulsion is prevented by inhibition of free fatty acid receptor GPR40. Circulation 2015;132:A15968.
23. Fettiplace MR, Kowal K, Ripper R, et al. Insulin signaling in bupivacaine-induced cardiac toxicity: sensitization during recovery and potentiation by lipid emulsion. Anesthesiology. 2016;124:428-42.