HDI is the Key to a (PICS)ture Perfect Life: The Role of High-Dose Insulin in Combating Poison-Induced Cardiogenic Shock

Fatimah Bah, Aradhna Chandra, Stella DeMars, Claire Faulkner, Anna Wisniewski | Jim Lane | Mahtomedi Senior High

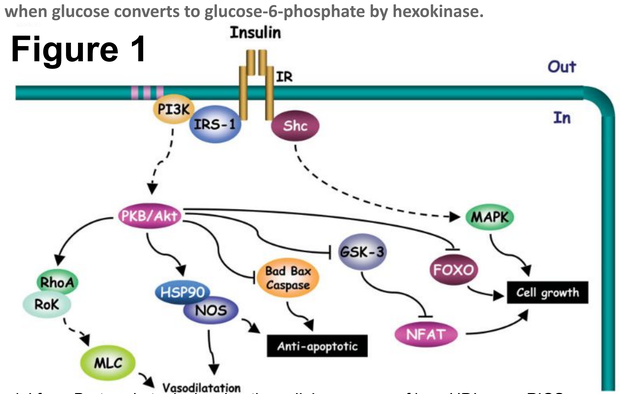
Abstract

Every year over 30,000 people are affected by Poison-Induced Cardiogenic Shock (PICS) as a result of Beta-Blockers and Calcium Channel Blockers. PICS can be treated by High-Dose Insulin(HDI) administered through a central venous catheter. After entering the heart, insulin is able to send signals to Insulin Receptor Substrate(IRS) 1 and 2 through insulin receptors, consisting of subunits *a* and *b* linked by disulfide bonds. Then IRS 1 and 2 are phosphorylated by activated receptors on multiple tyrosine residues that form binding sites for intracellular molecules containing Src-homology 2(SH2) domains. Thus, giving IRS 1 and 2 the ability to bind with the SH2 subunit of the phosphoinositide 3-kinase(PI3K) pathway. IRS 1 and 2 bind to a pocket of mainly hydrophilic amino acids in the SH2 subunit of the PI3K pathway. The primary interactions include bonds between phosphotyrosine and serine. Additionally, there are some bonds between hydrophobic amino acids in the pocket including an interaction between proline and glutamine. These bonds between IRS 1 and 2 and SH2 are important because they precipitate further interactions that take place, to ultimately save the heart and the patient from PICS. From there, a resulting increase in PI3K products promotes translocation of Glucose Transporter Type 4 (GLUT4) to the cardiomyocyte cell membrane, stimulating cardiac glucose uptake. This process is what allows for the heart's exclusive use of glucose as an energy source, which makes the heart return to homeostasis. The Mahtomedi Center for BioMolecular Modeling MAPS Team used 3D modeling and printing technology to investigate binding sites of IRS 1 and 2 in complex with the SH2 subunit of the P13K pathway and insulin receptors, in order to understand how HDI can save a patient suffering from PICS.

Cellular

Beta Blockers and Calcium Channel Blockers are treatments to help lower blood pressure. However, an overdose of these drugs can cause Poison Induced Cardiogenic Shock (PICS). Pics causes the heart to switch to free fatty acid oxidation which causes many complications. A cure for PICS is HIgh Dose Insulin. High Dose Insulin(HDI) causes the heart to switch from Free Fatty Acids(FFA) oxidation to glucose oxidation. Under normal conditions, the heart predominantly uses FFA as its preferred substrate for oxidation while inhibiting oxidation of other substrates. Instead of oxidizing glucose, the heart uses FFA in order to preserve glucose for other organs. When FFA oxidation occurs, acetyl-CoA is produced, creating citrate, a glycolysis inhibitor. During HDI treatment, the myocytes oxidize glucose, now the preferred substrate, due to the increase in insulin levels. The myocytes cause a decrease in FFA oxidation by inducing an increase in malonyl-COA, derived from acetyl-COA carboxylase. Malonyl-COA then is able to bind to the FFA oxidation enzyme, CPT-1. As a result, FFA transport proteins are no longer in use, and the heart now must oxidize glucose. To begin this process, insulin binds to the extracellular part of the insulin receptor (IR) enzyme, leading to the autotransphosphorylation of IR where one *b* subunit phosphorylates the other through tyrosine residues. After activation, IR phosphorylates other elements including the insulin receptor substrate (IRS) and the Shc protein. This results in activation of the phosphoinositide 3-kinase(PI3K) pathway, which contains the Sh2 domain. The Sh2 domain then binds to the phosphotyrosine residues of IRS. The increase of PI3K products, caused by this binding, leads to recruitment of phosphoinositide/ dependent kinase 1(PDK1) and protein kinase B (PKB/Akt). These enzymes are important for glucose uptake regulation in the heart with PI3K/PKB/Akt playing a key role in the translocation of GLUT4 to the cell membrane. When GLUT4 translocation occurs, it allows for glucose uptake into the cardiomyocytes. This begins the process of glycolysis when glucose converts to glucose-6-phosphate by hexokinase.

Figure 1



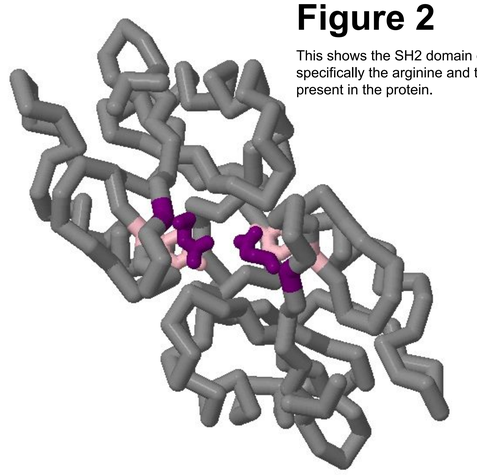
This is a model from Bertrand et al. showing the cellular process of how HDI cures PICS.

Molecular

The interaction between IRS 1 and 2 and the SH2 subunit of the PI3K pathway is a very crucial step in how HDI treats PICS. When IRS 1 and 2 bind to SH2, a cascade of reactions is set off that leads to the successful stimulation of cardiac glucose uptake and a healthy patient. IRS 1 and 2 bind to a mainly hydrophilic pocket of amino acids in the SH2 subunit of the PI3K pathway, specifically phosphotyrosyl sites bind with SH2. According to Wolf et. al, this mainly happens in three ways: “phosphatidylinositol 3-kinase, the phosphatase SH-PTP2, and Grb2, a linker protein.” Because of the phosphorylation of tyrosine molecules on SH2 that interacts with IRS 1 and 2, it can be determined that Grb2 is the primary SH2 containing protein that interacts with IRS 1 and 2. Through further investigation we have discovered that Tyrosine already present in SH2 is phosphorylated to become the phosphotyrosine. This is done through hydrogen and oxygen bonding in tyrosine molecules of SH2, which produces hydrogen peroxide. After the phosphotyrosine is formed through hydrogen peroxide induced phosphorylation, the IRS-1 is bound to the Grb2, and Grb2 is activated. The SH2 domain of GRB2 is mirrored and has a central opening with two tyrosine residues facing each other (see figure 2). Additionally, there are arginine residues surrounding the opening which is required for the binding of SH2 and IRS because in order for phosphotyrosine to bind with another molecule, arginine must be present to provide hydrogen bonds and assist in phosphorylation. Due to its symmetrical structure and the presence of arginine, we propose that IRS binds to GRB2 in the opening of the SH2 domain (see figure 2). According to Barnes and Gray, tyrosine is able to bind to proline side chains. IRS contains proline side chains on outer points of the protein, which is a convenient place for the tyrosine on SH2 to bind to because it is easily accessible and fits into the opening on SH2. Because of proline’s placement on IRS, we can assume that this is an optimal binding site for this interaction, which will inturn activates the entire GRB2 protein. The result of this binding sets off signaling through the PI3K pathway that allows for the further cellular interactions that ultimately stimulate glucose uptake and save the patient from PICS.

Figure 2

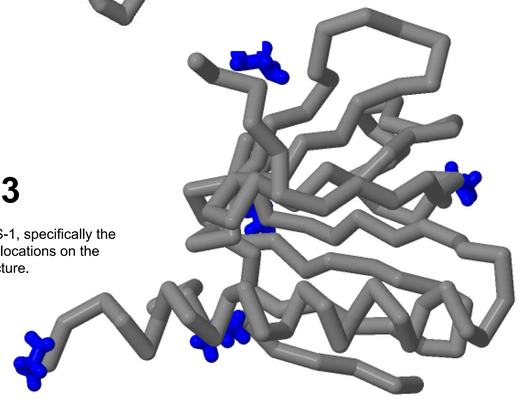
This shows the SH2 domain of the GRB2 protein, specifically the arginine and the tyrosine side chains present in the protein.



Key:
Pink- Tyrosine
Purple- Arginine
Blue- Proline

Figure 3

This shows the IRS-1, specifically the proline amino acid locations on the outside of the structure.



Application

The applications for high-dose insulin treatment used to treat Poison-Induced Cardiogenic Shock (PICS) are vast and greater than any currently being applied. In the medical field today, patients who are affected by PICS are first treated with saline, calcium, and glucagon despite the fact that these treatments rarely work to improve the status of a patient, are transient in nature, and are unable to treat different severities of PICS. Due to these complications, we propose using High-Dose Insulin (HDI) as a first course treatment for patients presenting with PICS. By implementing HDI as an immediate treatment resource for patients with PICS, the variability surrounding HDI no longer differs from patient to patient, and is a standard practice around the globe. Using HDI immediately for patients with PICS ensures the patient's heart returns to homeostasis quickly, reducing the time a patient's cardiovascular system is in distress. Our second proposal calls for doctors to taper a patient off of HDI as the standard of care, not cut a patient off abruptly. Physicians disagree on whether or not a patient should be cut off at one time a tapered off of HDI, but it is in a patient's best interest for the taper off method to become standard. Patients who are cut off cold turkey often require supplemental glucose for up to 24 hours after HDI concludes, and some patients may require a substantial 30 grams of supplemental glucose per hour in order to maintain homeostasis of the cardiovascular system. Tapering a patient off of HDI enables a physician to monitor a patient and minimize the excess glucose a patient needs. It’s in a patient’s and physician’s best interest to implement HDI as a standard, first course treatment for PICS, as well as tapering a patient off of HDI to see optimal results reflected in a patient's cardiovascular and overall health.

Conclusion

HDI should be utilized as the standard treatment for PICS. This influx of insulin enables the heart to shift from FFA oxidation to glucose oxidation because FFA oxidation is now inhibited. Binding between the SH2 subunit of GRB2 and IRS 1 allows for further interactions to take place that ultimately lead to glucose uptake into the cardiomyocytes. This stimulates glycolysis to begin and solidifies glucose as the main substrate for energy production in cardiomyocytes. The shift to glucose oxidation is integral in returning the heart to homeostasis because it requires less energy and increases the patient’s heart rate in order to alleviate complications associated with PICS. We propose tapering a patient off of HDI instead of an abrupt cessation in order to reduce variability in patient response and recovery, while also creating a higher standard of care. All in all, HDI is a potential life saving treatment if implemented as we've proposed.

References

Ando, A., et al. “A Complex of GRB2-Dynamin Binds to Tyrosine-Phosphorylated Insulin Receptor Substrate-1 after Insulin Treatment.” *The EMBO Journal*, vol. 13, no. 13, July 1994, pp. 3033–3038, https://doi.org/10.1002/j.1460-2075.1994.tb06602.x. Accessed 2 June 2022.

Barnes, Michael R, and Ian C Gray. *Bioinformatics for Geneticists*. Wiley, 18 Apr. 2003.

Bertrand, L., et al. “Insulin Signalling in the Heart.” *Cardiovascular Research*, vol. 79, no. 2, 30 Apr. 2008, pp. 238–248, https://doi.org/10.1093/cvr/cvn093. Accessed 1 Aug. 2020.

Chakraborty, Rebanta K., and Richard J. Hamilton. “Calcium Channel Blocker Toxicity.” *PubMed*, StatPearls Publishing, 2020, www.ncbi.nlm.nih.gov/books/NBK537147/.

Engebretsen, Kristin M., et al. “High-Dose Insulin Therapy in Beta-Blocker and Calcium Channel-Blocker Poisoning.” *Clinical Toxicology*, vol. 49, no. 4, Apr. 2011, pp. 277–283, crashingpatient.com/wp-content/uploads/2011/07/hiet-review.pdf, https://doi.org/10.3109/15563650.2011.582471. Accessed 22 Feb. 2019.

Hallak, H., et al. “Tyrosine Phosphorylation of Insulin Receptor Substrate-1 (IRS-1) by Oxidant Stress in Cerebellar Granule Neurons: Modulation by N-Methyl-D-Aspartate through Calcineurin Activity.” *Journal of Neurochemistry*, vol. 77, no. 1, 1 Apr. 2001, pp. 63–70, pubmed.ncbi.nlm.nih.gov/11279262/, https://doi.org/10.1046/j.1471-4159.2001.t01-1-00208.x. Accessed 1 Mar. 2023.

Klein, L.J., and F.C. Visser. “The Effect of Insulin on the Heart.” *Netherlands Heart Journal*, vol. 18, no. 4, 1 Apr. 2010, pp. 197–201, www.ncbi.nlm.nih.gov/pmc/articles/PMC2856868/.

Lee, C H, et al. “Nck Associates with the SH2 Domain-Docking Protein IRS-1 in Insulin-Stimulated Cells.” *Proceedings of the National Academy of Sciences*, vol. 90, no. 24, 15 Dec. 1993, pp. 11713–11717, www.ncbi.nlm.nih.gov/pmc/articles/PMC48054/pdf/pnas01531-0285.pdf, https://doi.org/10.1073/pnas.90.24.11713. Accessed 1 Mar. 2023.

--- “Nck Associates with the SH2 Domain-Docking Protein IRS-1 in Insulin-Stimulated Cells.” *Proceedings of the National Academy of Sciences*, vol. 90, no. 24, 15 Dec. 1993, pp. 11713–11717, www.ncbi.nlm.nih.gov/pmc/articles/PMC48054/pdf/pnas01531-0285.pdf, https://doi.org/10.1073/pnas.90.24.11713. Accessed 1 Mar. 2023.

Leonardini, Anna, et al. “Cross-Talk between PPARγand Insulin Signaling and Modulation of Insulin Sensitivity.” *PPAR Research*, vol. 2009, 2009, pp. 1–12, https://doi.org/10.1155/2009/818945.

Muoio, D. M., and C. B. Newgard. “Fatty Acid Oxidation and Insulin Action: When Less Is More.” *Diabetes*, vol. 57, no. 6, 28 May 2008, pp. 1455–1456, https://doi.org/10.2337/db08-0281. Accessed 3 Feb. 2020.

Myers, M G, et al. “Role of IRS-1-GRB-2 Complexes in Insulin Signaling.” *Molecular and Cellular Biology*, vol. 14, no. 6, June 1994, pp. 3577–3587, https://doi.org/10.1128/mcb.14.6.3577-3587.1994. Accessed 1 Feb. 2023.

Rao, G. N. “Hydrogen Peroxide Induces Complex Formation of SHC-Grb2-SOS with Receptor Tyrosine Kinase and Activates Ras and Extracellular Signal-Regulated Protein Kinases Group of Mitogen-Activated Protein Kinases.” *Oncogene*, vol. 13, no. 4, 15 Aug. 1996, pp. 713–719, pubmed.ncbi.nlm.nih.gov/8761292/. Accessed 1 Mar. 2023.

Wolf, Gert, et al. “PTB Domains of IRS-1 and Shc Have Distinct but Overlapping Binding Specificities (*).” *Journal of Biological Chemistry*, vol. 270, no. 46, 17 Nov. 1995, pp. 27407–27410, www.sciencedirect.com/science/article/pii/S0021925818879686, https://doi.org/10.1074/jbc.270.46.27407. Accessed 1 Mar. 2023.

Woodward, Christina, et al. “High Dose Insulin Therapy, an Evidence Based Approach to Beta Blocker/Calcium Channel Blocker Toxicity.” *DARU Journal of Pharmaceutical Sciences*, vol. 22, no. 1, 2014, p. 36, www.ncbi.nlm.nih.gov/pmc/articles/PMC3985540/, https://doi.org/10.1186/2008-2231-22-36.

Zhu, Yi, et al. “Cardiac PI3K-Akt Impairs Insulin-Stimulated Glucose Uptake Independent of MTORC1 and GLUT4 Translocation.” *Molecular Endocrinology*, vol. 27, no. 1, Jan. 2013, pp. 172–184, www.ncbi.nlm.nih.gov/pmc/articles/PMC3545208/, https://doi.org/10.1210/me.2012-1210. Accessed 1 Mar. 2023.