

Comparison of the Hypoglycemic Effects of Erythropoietin and U-74389G on Glucose Levels

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Abstract

Aim: This study calculated the hypoglycemic capacities of 2 drugs: the erythropoietin (Epo) and the antioxidant drug U-74389G. The calculation was based on the results of 2 preliminary studies, each one of which estimated the hypoglycemic influence, after the respective drug usage in an induced hypoxia reoxygenation animal experiment.

Materials and Methods: The 2 main experimental endpoints at which the glucose (GI) levels were evaluated was the 60th reoxygenation min (for the groups A, C and E) and the 120th reoxygenation min (for the groups B, D and F). Specially, the groups A and B were processed without drugs, groups C and D after Epo administration; whereas groups E and F after U-74389G administration.

Results: The first preliminary study of Epo presented a non significant hypoglycemic effect by 0.84%±1.12% (p-value=0.4430). The second preliminary study of U-74389G presented a significant hypoglycemic effect by 3.94%±1.06% (p-value=0.0005). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that U-74389G has 4.660603-fold more hypoglycemic potency than Epo (p-value=0.0000).

Conclusions: The anti-oxidant capacities of U-74389G enhance the acute hypoglycemic properties presenting 4.660603-fold more intensive hypoglycemia than Epo (p-value=0.0000).

Keywords: hypoxia; erythropoietin; U-74389G; glucose levels; reoxygenation

INTRODUCTION

U-74389G is not famous for its hypoglycemic¹ capacity (p-value=0.0005). U-74389G as a novel antioxidant factor, implicates exactly only 255 published studies. The hypoxia reoxygenation (HR) type of experiments was noted in 4.31% of these studies. A tissue protective feature of U-74389G was obvious in these HR studies. The U-74389G chemically known as 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-

3,20-dione maleate salt is an antioxidant complex, which prevents the lipid peroxidation either iron-dependent, or arachidonic acid-induced one. Animal kidney, liver, brain microvascular endothelial cells monolayers and heart models were protected by U-74389G after HR injury. U-74389G also attenuates the leukocytes; down-regulates the proinflammatory gene; treats the endotoxin shock; produces cytokine; enhances the mononuclear immunity; protects the endothelium and presents antishock property.

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Erythropoietin (Epo) even if is not famous for its hypoglycemic action (p-value=0.4430), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 29,943 published biomedical studies, only a 10.51% of them negotiate the known type of HR experiments. Nevertheless, Epo as a cytokine, it is worth of being studied about glucose levels too.

This experimental work tried to compare the hypoglycemic effects of the above drugs on a rat induced HR protocol. They were tested by calculating the serum glucose (Gl) levels declines.

MATERIALS AND METHODS

Animal Preparation

The Vet licenses under 3693/12-11- 2010 & 14/10-1-2012 numbers, the granting company and the experiment location are mentioned in preliminary references^{1,2}. The human animal care of Albino female Wistar rats, the 7 days pre-experimental *ad libitum* diet, the non-stop intra-experimental anesthesiologic techniques, the acidometry, the electrocardiogram and the oxygen supply and post-experimental euthanasia are also described in preliminary references. Rats were 16 – 18 weeks old. They were randomly assigned to six (6) groups consisted in N=10. The stage of 45 min hypoxia was common for all 6 groups. Afterwards, reoxygenation of 60 min was followed in group A; reoxygenation of 120 min in group B; immediate Epo intravenous (IV) administration and reoxygenation of 60 min in group C; immediate Epo IV administration

and reoxygenation of 120 min in group D; immediate U-74389G IV administration and reoxygenation of 60 min in group E; and immediate U-74389G IV administration and reoxygenation of 120 min in group F. The dose height assessment for both drugs are described at preliminary studies as 10 mg/Kg body mass.

Hypoxia was caused by laparotomic clamping the inferior aorta over renal arteries with forceps for 45 min. The clamp removal was restoring the inferior aorta patency and reoxygenation. After exclusion of the blood flow, the protocol of HR was applied, as described above for each experimental group. The drugs were administered at the time of reperfusion; through inferior vena cava catheter. The Gl levels (Gls) were determined at 60th min of reoxygenation (for A, C and E groups) and at 120th min of reoxygenation (for B, D and F groups). However, the predicted Gls values were used since a very powerful relation was risen with animals' mass (p-value=0.0319).

STATISTICAL ANALYSIS

Table 1 presents the (%) hypoglycemic influence of Epo regarding reoxygenation time. Also, Table 2 presents the (%) hypoglycemic influence of U-74389G regarding reoxygenation time. Chi-square tests were applied using the ratios which produced the (%) results per endpoint. The outcomes of chi-square tests are depicted at Table 3. The statistical analysis was performed by Stata 6.0 software [Stata 6.0, StataCorp LP, Texas, USA].

Table 1. *The (%) hypoglycemic influence of erythropoietin in connection with reoxygenation time*

Hypogluccemia	±SD	Reoxygenation time	p-value
-0.03%	±8.28%	1h	0.9904
-1.56%	±6.79%	1.5h	0.3549
-3.15%	±5.46%	2h	0.1509
+1.56%	±7.31%	reperfusion time	0.3721
-0.84%	±1.12%	interaction	0.4430

Table 2. *The (%) hypoglycemic influence of U-74389G in connection with reoxygenation time*

Hypogluccemia	±SD	Reoxygenation time	p-value
-5.28%	±8.03%	1h	0.0663
-7.08%	±6.78%	1.5h	0.0001
-8.88%	±5.09%	2h	0.0003
+1.41%	±6.43%	reperfusion time	0.4103
-3.94%	±1.06%	interaction	0.0005

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Table 3: The U-74389G / erythropoietin efficacies ratios on glucose levels hypoglycemia after chi-square tests application

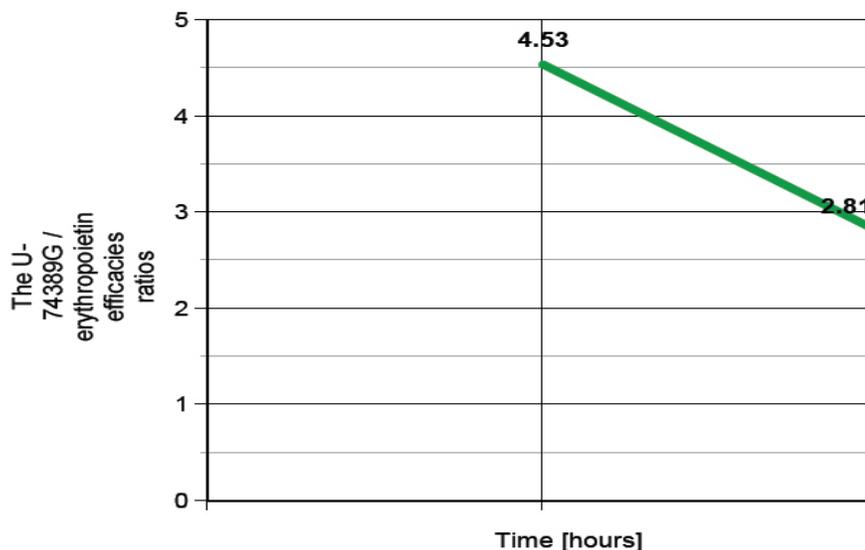
Odds ratio	[95% Conf. Interval]		p-values	Endpoint
156.4991	156.2428	156.7558	0.0000	1h
4.53659	4.532788	4.540395	0.0000	1.5h
2.81397	2.808338	2.819613	0.0000	2h
0.9073196	0.9063179	0.9083224	0.0000	reperfusion time
4.660603	4.655341	4.665871	0.0000	interaction

RESULTS

The successive application of chi-square tests revealed that U-74389G accentuated the hypoglycemia by 156.4991-fold [156.2428-156.7558] than Epo at 1h, by 4.53659-fold [4.532788-4.540395] at

1.5h, by 2.81397-fold [2.808338-2.819613] at 2h, by 0.9073196-fold [0.9063179-0.9083224] without drugs and by 4.660603-fold [4.655341-4.665871] whether all variables have been considered (p-value=0.0000).

The U-74389G / erythropoietin efficacies ratios on glucose levels hypoglycemia



<https://nces.ed.gov/nceskids/createagraph/default.aspx?ID=302c6bb1e7834fa4ab068fe17e01fabf>

DISCUSSION

The unique available study investigating the hypoglycemic effect of U-74389G on GIs was the preliminary one¹. Although the most famous activities of neuroprotection and membrane-stabilization properties, it accumulates in the cell membrane, protecting vascular endothelium from peroxidative damage but hardly penetrates the blood-brain barrier. It elicits a beneficial effect in ototoxicity and Duchenne muscular dystrophy. It increases γ GT, SOD, and GSH levels in oxygen-exposed cells. It treats septic states and acts as immunosuppressant in flap survival. It prevents the learning impairments, it delays the early synaptic transmission decay during

hypoxia improving energetic state of neurons. It shows antiproliferative properties on brain cancer cells and is considered as a new promising anti inflammatory drug for the treatment of reperfusion syndrome in IR injuries.

The same authors confirmed² the short-term hypoglycemic effect of Epo preparations in non iron deficient individuals. Zhang C et al demonstrated³ that vorinostat, a class I/IIb/IV histone deacetylase inhibitors potently inhibits HIF- α nuclear translocation via direct acetylation of its associated chaperone, heat shock protein 90, associated with downregulation of downstream hypoxia molecules such as Epo, glucose transporter 1. Pang Y et al prevented⁴ the binding of

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hypoxia-inducible factor 1 and 2 (HIF-1 and HIF-2) to the hypoxia response element (HRE) sites on DNA. This resulted in reduced transcriptional activation of HIF target genes, including EPO, phosphoglycerate kinase 1 (PGK1), endothelin 1 (EDN1), glucose transporter 1 (GLUT1), lactate dehydrogenase A (LDHA), and vascular endothelial growth factor (VEGFA), which consequently inhibited the growth of metastatic pheochromocytomas. Ashok BS et al found⁵ that hypoxia-inducible factor-1 alpha (HIF-1 α) has a major role in the cellular adaptation by inducing the expression of several proteins, including vascular endothelial growth factor, Epo and inducible nitric oxide synthase. Koivunen P et al described⁶ hypoxia-inducible factor prolyl 4-hydroxylases (HIF-P4Hs) as enzymes that act as cellular oxygen sensors, capable to induce Epo. HIF stabilization driven changes in gene expression reprogram metabolism to promote glucose intake and glycolysis over oxidative metabolism and to reduce inflammation. Sano M et al treated⁷ with the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapaglifloz patients with diabetes and allowed fibroblasts to resume normal Epo production which reaches a plateau in 2 - 4 weeks; whereas the proximal tubules are overtaxed by excessive glucose reabsorption. Ding J et al shown⁸ that carbamylated Epo (CEPO) acts upon a heteroreceptor complex comprising both the Epo receptor and the common β receptor subunit (β cR, also known as CD131). The blockage of CD131 reduced CEPO-mediated glial cell line-derived neurotrophic factor (GDNF) production, while GFR receptor blockage and GDNF neutralization inhibited CEPO-induced neurogenesis. Farsijani NM et al associated⁹ suppression of renal Epo production with increased glucose uptake, enhanced glycolysis and reduced mitochondrial mass. Brigandi RA et al stimulated¹⁰ endogenous Epo synthesis by hypoxia-inducible factor-prolyl hydroxylase inhibitors (PHIs) and induced effective erythropoiesis by non-EPO effects. GSK1278863 is an orally administered small-molecule PHI which also induces an effective Epo response and stimulates non-Epo mechanisms for erythropoiesis by 25.35% at least in anemic chronic kidney disease patients. Lindholm ME et al confirmed¹¹ that target genes of HIF-1 increase oxygen transport through

mechanisms such as Epo-mediated erythropoiesis and vascular endothelial growth factor-induced angiogenesis and improve tissue function during low oxygen availability through increased expression of glucose transporters and glycolytic enzymes. Lykov AP et al found¹² that Epo abolishes suppression of cell proliferation in culture with normal glucose level, while under hyperglycemia, inhibition of cell proliferation becomes more pronounced in hypoxic bone marrow multipotent mesenchymal stromal cells from Wistar rats. Ryou MG et al concluded¹³ that methylene blue enhances HIF-1 α protein content accompanied by an activation of the Epo signaling pathway in hippocampus. Pelster B et al discussed¹⁴ Hif-3 α as a competitive inhibitor of Hif-1 α and Hif-2 α in mammalian cells or tissues. The Hif signaling pathway is tightly connected to cell circuitries such as glucose and lipid metabolism; since some of the downstream genes of the Hif signaling pathway, namely, Epo and vascular endothelial growth factor, are known to be clock controlled as well. Caris AV et al noticed¹⁵ Epo and Gls elevated post-exercise than baseline pre-exercise in the hypoxia + carbohydrate group. Chen RL et al show¹⁶ that 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetic acid (IOX3), a selective small molecule (280.66 Da) HIF prolyl hydroxylase inhibitor, could up-regulate HIF-1 α and increase Epo expression in mouse IR brains. Zhang Q et al observed¹⁷ increased HIF-1 α , Epo and VEGF levels associated with the activation of PI3K/Akt signaling. Reischl S et al inhibited¹⁸ PHD activity which resulted in HIF-1 α stabilization. The novel PHD inhibitor FG-4497 induces the HIF signaling pathway, leading to increased VEGF and Epo expression in mice. Souvenir R et al found¹⁹ that Epo, as a downstream gene of HIF, inhibits HIF-1 α in a dose-dependent manner in an in vitro model of hypoxia-ischemia during oxygen and Gl deprivation. Zhang Z et al demonstrated²⁰ that pretreatment with NAC increased protein levels of hypoxia-inducible factor-1 α (HIF-1 α), the regulatable subunit of HIF-1 and its target proteins Epo and Gl transporter (GLUT)-3 in rodents subjected to cerebral IR. Kontani S et al described²¹ the protein expression levels of heme oxygenase 1, Epo and Gl transporter-3, as genes downstream of hypoxia-inducible factor 1 α (HIF-1 α) regulated by the oxygen-

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dependent hydroxylation of proline residues by prolyl hydroxylases (PHDs). Spliethoff K et al found²² that individuals with low baseline insulin sensitivity and Epo levels were more susceptible to acute mountain sickness. Singh M et al observed²³ an increase in HIF1 (hypoxia inducible factor-1) and its regulated genes; Epo, vascular endothelial growth factor, and Gl transporter-1 in A549 cell line. Jones SM et al suggested²⁴ that HIF-induced Epo, released from astrocytes, protects neurons from oxygen-Gl deprivation OGD in astrocyte cultures. Knaup KX et al found²⁵ that prominent HIF-regulated target genes such as the vascular endothelial growth factor (VEGF), the Gl transporter 1 (Glut-1), or Epo help cells and organisms to survive in a low oxygenated environment. Dong Y et al revealed²⁶ that the expression of HIF-1 α and its downstream effectors, vascular endothelial growth factor (VEGF), Epo and Gl transporter 1 (GLUT1), were increased in the hippocampus 48h after the induction of subarachnoid hemorrhage SAH in Sprague-Dawley (SD) rats. Lundgrin EL et al detected²⁷ PAH with fasting 2-deoxy-2-[(18)F]fluoro-d-glucose positron emission tomography (FDG-PET) since PAH hearts have pathologic glycolytic metabolism and Gl uptake is informative for cardiac function; however, FDG uptake in the right ventricle was not correlated with Epo. Vortmeyer AO et al caused²⁸ accumulation and activation of hypoxia inducible factor (HIF) which is followed by expression of VEGF, Epo, nitric oxide synthase and Gl transporter 1 in a germline mutation of the Von Hippel-Lindau (VHL) tumor-suppressor gene. Weinreb O et al discussed²⁹ novel molecules exerting antioxidant/monoamine oxidase inhibition, activation of the hypoxia-inducible factor (HIF)-1 signaling pathway, induction of HIF-1 target iron-regulatory and antioxidative genes in Parkinson's disease. Agani F et al calculated³⁰ the number of HIF-1 and hypoxia-regulated target genes as growing exponentially and includes genes that encode proteins with roles in erythropoiesis, angiogenesis, glycolytic pathway, Gl transport, metastasis, and cell survival. Chiang CK et al observed³¹ decreased Epo (a representative HIF target gene) expression also in HepG2 overexpressing UPR

activating transcription factor (ATF)4. Transcriptional activity of the Epo3'-enhancer, which is mainly regulated by HIF, was abolished by both ER stressors and ATF4 overexpression. A novel ATF4 binding site (TGACCTCT) within the Epo 3'-enhancer region suggests a distinct role for ATF4 in UPR-dependent suppression of the enhancer. Tang Z et al found³² silencing aquaporin4 (AQP4) expression using small interfering ribonucleic acid for AQP4 to block astrocytic swelling. Inhibition of the over-activation of mitogen-activated protein kinase pathway (MAPK) mitigated the plasma membrane (PM) AQP4 overabundance and cellular swelling. As expected, treatment with rhEPO significantly reduced the OGD followed by reoxygenation increase in cell volume, morphological swelling, and mitochondrial swelling as well as the up-regulation of AQP4 in PM. Fan X et al estimated³³ a borderline additive effect of Epo when combined with hypothermia at 26% in a rat model of neonatal HI. Chrysikos DT et al examined³⁴ any effects of U-74389G whereas Gl was not significantly different in a swine model of pancreatic IR. Vlkolinský R et al revealed³⁵ protective activity after 21-aminosteroid U-74389G (10 μ M) on synaptic transmission recovery and on t1/2 during hypoxia in rat hippocampal slices CA1 neurons exposed to hypoxia (HYP) combined with lowered D-glucose concentration. Di Monte DA et al assessed³⁶ astrocytes as the site of bioactivation of the parkinsonism-inducing agent 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) into its toxic 1-methyl-4-phenylpyridinium (MPP(+)) metabolite. The lazaroid antioxidant U-74389G was not capable of restoring glutamate net uptake. The effect of MPP(+) on glutamate clearance was accompanied by a decrease in cellular ATP; and could be enhanced by withdrawing Gl from the incubation medium or by inhibiting glycolysis with 2-deoxyglucose.

According to above, table 3 shows that U-74389G accentuated by 4.660603-fold [4.655341-4.665871] the hypoglycemic potency than Epo (p-value=0.0000); a trend attenuated along time, in Epo non-deficient rats. A meta-analysis of these ratios from the same experiment, for 12 other seric variables, provides comparable results (table 4)³⁷.

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Table 4: A U-74389G / erythropoietin efficacies ratios meta-analysis on 12 hematologic variables (10 variables with balancing efficacies and 2 variables with opposite efficacies)¹.

Endpoint Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
WBC	0.957451	0.3782	1.396122	0.0000	1.918237	0.0000	1.71622	0.0000	1.601887	0.0000
Hematocrit	38.424	0.0000	9.076658	0.0000	6.222898	0.0000	1.001356	0.2184	12.66419	0.0000
Hemoglobin	1.268689	0.0000	1.839035	0.0000	13.1658	0.0000	1.252422	0.0000	1.94889	0.0000
RBC count	0.961059	0.0000	1.733395	0.0000	6.519657	0.0000	1.039524	0.0000	1.309673	0.0000
RbcDW	3.306773	0.0000	3.023389	0.0000	2.655885	0.0000	0.2259914	0.0000	2.370353	0.0000
Platelet count	2.42839	0.0000	6.00238	0.0000	6.1333429	0.0000	3.939027	0.0000	37.62979	0.0000
MPV	145.8532	0.0000	4.053619	0.0000	2.603947	0.0000	1.2334644	0.0000	4.164431	0.0000
Platelet DW	0.6940233	0.0000	1.319118	0.0000	2.206972	0.0000	2.2484006	0.0000	2.458888	0.0000
Creatinine	168.9034	0.0000	4.872332	0.0000	3.039572	0.0000	1.0262016	0.0000	5.005523	0.0000
Total proteins	155.9562	0.0000	4.421079	0.0000	2.803573	0.0000	0.8842162	0.0000	4.541934	0.0000
Mean	7.91129943	0.0378	3.10924261	0.0000	3.90159936	0.0000	1.1749027	0.0218	4.01004182	0.0000

Endpoint Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
Mean corpuscular hemoglobin concentrations	-0.2774225	0.0000	-0.5504722	0.0000	-0.8522433	0.0000	+3.044774	0.0000	-0.7793243	0.0000
Platelet crit	-0.2312044	0.0000	-0.6719365	0.0000	-1.330756	0.0886	5.620077	0.0000	-0.9771515	0.0000
Mean	-0,2532076	0.0000	-0,6081795	0.0000	-1,0649544	0.0443	4,1366488	0.0000	-0,8726499	0.0000

CONCLUSION

The anti-oxidant agent U-74389G was proved also more hypoglycemic by 4.660603-fold [4.655341-4.665871] than Epo (p-value=0.0000) in rats. However, this trend is attenuated along the short term time frame of the experiment. A biochemical investigation remains about whether the Hif factor also mediates in these actions for the U-74389G.

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