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The Effect of Erythropoietin on Total Protein Levels during Ischemia Reperfusion Injury in Rats

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Abstract

Aim: The aim of this experimental study was to examine the effect of erythropoietin on rat model and particularly in an ischemia-reperfusion (IR) protocol. The beneficial effect or non-effectiveness of that molecule was studied biochemically using blood mean total protein levels.

Materials and Methods: 40 rats of mean weight 247.7 g were used in the study. Total protein levels were measured at 60 min (groups A and C) and 120 min (groups B and D) of reperfusion. Erythropoietin was administered in groups C and D.

Results: Epo administration non-significantly decreased the predicted TP levels by 1.27% ± 1.51% (p=0.3721). Reperfusion time non-significantly increased the predicted TP levels by 1.27% +1.51% (p=0.3549). However, erythropoietin administration and reperfusion time together produced a non-significant combined effect in decreasing the predicted TP levels by 0.68% ± 2.48% (p=0.4430).

Conclusions: Erythropoietin administration interacted or not with reperfusion time has non-significant short – term decreasing effects on blood total protein levels.

Keywords: Ischemia; Erythropoietin; Total protein; Reperfusion

Introduction

Tissue ischemia and reperfusion (IR) remain one of the main causes of permanent or transient damage with serious implications on adjacent organs and certainly on patients' health. The use of erythropoietin (Epo) has been a research subject for a lot of years. However, even if important progress has been made, satisfactory answers have not been given yet to fundamental questions, as, by what velocity this factor acts, when should it be administered, and in which dosage. The particularly satisfactory action of Epo in stem blood cells recovery has been noted in several performed experiments. After a careful literature search (PubMed - Medline), it was realized that this certain growth factor has been tried in IR experiments. de Los Milagros Bassani et al. [1] considered large scale, transient gene expression, highly dependent on the physiological status of a cell line. This corresponded to 10% of the total protein (TP) concentration in the cell-free supernatant of cultures in protein-free medium based on two different bicistronic model plasmids expressing rHuEPO. Up to 30% higher transfect abilities were found for cells of early passages compared to those from late passages under protein-free culture conditions. Shirole et al. [2] inhibited TP levels in lung homogenates and reduced the respiratory flow due to gasping dose dependently (7.5, 15 and 30 mg/kg i.p.) treating with essential oil of Pistacia integerrima J.L. Stewart ex Brandis galls (EOPI) ovalbumin sensitized guinea pigs. Aizawa et al. [3] suppressed increased urinary TP of Thy-1 induced mesangial proliferative glomerulonephritis (Thy-1-GN), 6 days after epoetin β pegol (continuous erythropoietin receptor activator, CERA), - a long-acting erythropoiesis-stimulating agent (25 μg/kg) - IV administration 4 h before anti-Thy1.1 antibody injection, proving a renoprotective effect in rats. Yang et al. [4] found limited evidence to suggest that nandrolone decanoate can increase plasma TP (MD 0.40 g/L, 95% CI 0.13 to 0.67), levels compared with Epo. Ruskovska et al. [5] found TP carbonyls reduced by vitamin C supplementation (2 × 500 mg vitamin C per day for 4 weeks) either under or not Epo dialysis in end-stage renal disease patients than control ones. The present authors found the influence of Epo administration (Table 1) on some serum hematologic and biochemic variables levels 1 h, 1.5 h, 2 h and interaction of Epo with reperfusion time after ischemia removal in related rats IR injury experiments.

The aim of this experimental study was to examine the effect of Epo on rat model and particularly in a liver IR protocol since liver is the main location of TP production. The beneficial effect or non-effectiveness of that molecule was studied by measuring the blood mean TP levels.

Materials and Methods

Animal preparation

This experimental study was laid out at the Experimental Research Center of ELPEN Pharmaceuticals Co. Inc. S.A. at Pikermi, Attiki. All settings needed for the study including consumables, equipment and substances used, were a courtesy of that S. A. Wistar albino rats were used in accordance with accepted standards of humane animal care. They were housed in laboratory 7 days before the experiment with easy access to water and food. The experiment was acute, that is, the animal usage was completed following experimental set of times without awakening and preservation of the rodents. They were randomly assigned to four experimental groups (10 animals in each group): 1)

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Variable	1 h rep	p-value	1.5 h rep	p-value	2 h rep	p-value	interaction of Epo and rep	p-value
white blood cells [17]	± 24.01% ± 13.38%	0.1012	± 22.09% ± 9.11%	0.0351	± 20.17% ± 12.94%	0.0902	± 14.63% ± 5.40%	0.0080
mean corpuscular hemoglobin [18]	± 0.01% ± 1.29%	0.9904	± 0.67% ± 0.80%	0.3549	± 1.34% ± 1.08%	0.1509	-0.36% ± 0.47%	0.4430
platelet distribution width [19]	± 1.60% ± 0.80%	0.0765	± 1.36% ± 0.58%	0.0205	± 1.13% ± 0.74%	0.1152	± 0.37% ± 0.37%	0.0615
plateletcrit [20]	-16.47% ± 10.40%	0.0921	-13.74% ± 7.01%	0.0158	-11.01% ± 7.34%	0.0882	-6.88% ± 3.69%	0.0615
uric acid [21]	± 10.13% ± 15.10%	0.4917	± 15.86% ± 10.21%	0.1408	± 21.59% ± 15.45%	0.1940	± 9.33% ± 6.16%	0.1264
alkaline phosphatase [22]	± 0.20% ± 18.57%	0.9904	± 10.70% ± 12.78%	0.3549	± 21.20% ± 17.11%	0.1509	± 5.79% ± 7.72%	0.4430
CPK [23]	± 0.15% ± 14.09%	0.9904	± 7.91% ± 9.44%	0.3549	± 15.67% ± 12.65%	0.1509	± 4.28% ± 5.70%	0.4430
LDH [24]	± 0.08% ± 7.92%	0.9904	± 4.48% ± 5.35%	0.3549	± 8.89% ± 7.17%	0.1509	± 2.42% ± 3.22%	0.4430
sodium [35]	± 0.72% ± 0.74%	0.3054	± 0.21% ± 0.63%	0.7136	-0.29% ± 1.09%	0.7670	-0.11% ± 0.38%	0.7531
progesterone [36]	-0.20% ± 18.65%	0.9904	-8.86% ± 10.58%	0.3549	-17.53% ± 14.15%	0.1509	-4.79% ± 6.39%	0.4430

Table 1: The erythropoietin (Epo) influence (± SD) on the levels of some hematologic and biochemic variables concerning reperfusion (rep) time.

Ischemia for 45 min followed by reperfusion for 60 min (group A); 2) Ischemia for 45 min followed by reperfusion for 120 min (group B); 3) Ischemia for 45 min followed by immediate Epo intravenous (IV) administration and reperfusion for 60 min (group C); 4) ischemia for 45 min followed by immediate Epo IV administration and reperfusion for 120 min (group D).

The Epo dose was 10 mg/Kg body weight of animals. The animals were submitted into prenarcosis at first of experiment, followed by general anesthesia. Their electrocardiogram and acidometry were continuously monitored. Their inferior aorta flow was excluding by forceps. After exclusion, the protocol of liver IR was applied, hampering further liver TP production. The molecules were administered at the time of ischemia removal, through inferior vena cava, after catheterization had been achieved. The TP measurement was performed at 60 min of reperfusion (groups A and C) and 120 min of reperfusion (groups B and D).

Rats were submitted into general anesthesia by initial intramuscular (IM) administration of 0.5 cc compound, which constituted of 0.25 cc xylazine, [25 cc, 20 mg/cc] and 0.25 cc ketamine hydrochloride [1000, 100 mg/cc, 10cc]. Before initiation of laparotomy, 0.03 cc butorphanol [10 mg/cc, 10cc] anesthetic agent was administered subcutaneously (SC). Continuous oxygen supply was administered during whole experiment performance. Ischemia was caused by clamping inferior aorta for 45 min after laparotomic access was achieved. Reperfusion was induced by removing the clamp and reestablishment of inferior aorta patency. Forty (40) Wistar albino rats of mean weight 247.7 g [Std. Dev: 34.99172 g] were used, of min weight ≥ 165 g and max weight < 320 g. Rats' weight could be potentially a confusing factor, e.g. fatter rats to have greater blood TP levels. This suspicion will be investigated.

Model of ischemia-reperfusion injury

Control groups: 20 control rats of mean weight 252.5 g [Std. Dev: 39.31 g] were subjected to ischemia for 45 min followed by reperfusion.

Group A

Reperfusion which lasted 60 min concerned 10 control rats of mean weight 243 gr [Std. Dev: 45.77 gr] and mean TP levels 5.34 gr/dl [Std. Dev: 0.60 gr/dl] (Table 2).

Group B

Reperfusion which lasted 120 min concerned 10 control rats of mean weight 262 gr [Std. Dev: 31.10 gr] and mean TP levels 5.82 gr/dl [Std. Dev: 0.64 gr/dl] (Table 2).

Group	Variable	Mean	Std. Dev
A	Weight	243 gr	45.77 gr
mean corpuscular hemoglobin [18]	± 0.01% ± 1.29%	0.9904	± 0.67% ± 0.80%
platelet distribution width [19]	± 1.60% ± 0.80%	0.0765	± 1.36% ± 0.58%
plateletcrit [20]	-16.47% ± 10.40%	0.0921	-13.74% ± 7.01%
uric acid [21]	± 10.13% ± 15.10%	0.4917	± 15.86% ± 10.21%
alkaline phosphatase [22]	± 0.20% ± 18.57%	0.9904	± 10.70% ± 12.78%
CPK [23]	± 0.15% ± 14.09%	0.9904	± 7.91% ± 9.44%
LDH [24]	± 0.08% ± 7.92%	0.9904	± 4.48% ± 5.35%
sodium [35]	± 0.72% ± 0.74%	0.3054	± 0.21% ± 0.63%
progesterone36	-0.20% ± 18.65%	0.9904	-8.86% ± 10.58%

Table 2: Weight and total protein levels and Std. Dev. of groups.

Erythropoietin group

20 Epo rats of mean weight 242,9 gr [Std. Dev: 30.31 gr] were subjected to ischemia for 45 min followed by reperfusion in the beginning of which 10 mg Epo /kg body weight were IV administered.

Group C

Reperfusion which lasted 60 min concerned 10 Epo rats of mean weight 242.8 gr [Std. Dev: 29.33 gr] and mean TP levels 5.31 gr/dl [Std. Dev: 0.47 gr/dl] (Table 2).

Group D

Reperfusion which lasted 120 min concerned 10 Epo rats of mean weight 243 gr [Std. Dev: 32.84 gr] and mean TP levels 5.18 gr/dl [Std. Dev: 0.49 gr/dl] (Table 2).

Results

Weight comparison of each one from 4 rats groups initially was performed with other one from 3 remained groups applying statistical paired t-test (Table 3). Any emerging significant difference among TP levels will be investigated whether owed in the above mentioned significant weight correlations. TP levels comparison of each one from 4 rats groups initially was performed with other one from 3 remained groups applying statistical paired t-test (Table 3). Applying generalized linear models (glm) with dependant variable the TP levels and independent variables the Epo administration or no, the reperfusion time and their interaction, resulted in: Epo administration significantly decreased the TP levels by 0.33 gr/dl [-0.70 gr/dl - 0.03 gr/dl] (P=0.0719). This finding was in accordance with the results of

DG	Variable	Difference	p-value
A-B	Weight	-19 gr	0.2423
	TP	-0.48 gr/dl	0.1090
A-C	Weight	0,2 gr	0.9900
	TP	0.03 gr/dl	0.8818
A-D	Weight	0 gr	1.0000
	TP	0.16 gr/dl	0.4054
B-C	Weight	19.2 gr	0.2598
	TP	0.51 gr/dl	0.0879
B-D	Weight	19 gr	0.1011
	TP	0.64 gr/dl	0.0304
C-D	Weight	-0.2 gr	0.9883
	TP	0.13 gr/dl	0.3821

Table 3: Statistical significance of mean values difference for groups (DG) after statistical paired t test application.

			P-Values	
Decrease	95% c. in.	Reperfusion	-test	glm
-0.03 gr/dl	-0.53 gr/dl	1 h	0.008	0.9027
-0.335 gr/dl	-0.70 gr/dl	1.5 h	0.0220	0.0719
-0.64 gr/dl	-1.17 gr/dl	2 h	0.0304	0.0226
± 0.175 gr/dl	-0.20 gr/dl	reperfusion time	0.2992	0.3547
0.2063637gr/dl	-0.42 gr/dl			0.0657

Table 4: The decreasing influence of erythropoietin in connection with reperfusion time.

Groups	Variable	Std. Dev
A	5.37 gr/dl	0.33 gr/dl
B	5.51 gr/dl	0.22 gr/dl
C	5.37 gr/dl	0.21 gr/dl
D	5.37 gr/dl	0.23 gr/dl

Table 5: Mean predicted total protein values adjusted for weight and Std. Dev. of groups.

paired t-test (p=0.0220). Reperfusion time non-significantly increased the TP levels by 0.17 gr/dl [-0.20 gr/dl - 0.55 gr/dl] (p=0.3547), also in accordance with paired t-test (p=0.2992). However, erythropoietin administration and reperfusion time together produced a non-significant combined effect in decreasing the TP levels by 0.20 gr/dl [-0.42 gr/dl - 0.01 gr/dl] (P= 0.0657). Reviewing the above Table 3 and 4 sums up concerning the alteration influence of Epo in connection with reperfusion time. Inserting the rats weight as independent variable at glm, a significant relation turns on TP levels (p=0.0057), so as to further investigation is needed. The predicted TP values, adjusted for rats weight were calculated (Table 5). Afterwards, the predicted TP values of everyone from 4 rats groups were compared each other from 3 remained groups applying statistical paired t-test (Table 6). Applying generalized linear models (glm) with dependant variable the predicted TP levels and independent variables the Epo administration or no, the reperfusion time and their interaction, resulted in: Epo administration non-significantly decreased the predicted TP levels by 0.06 gr/dl [-0.09 gr/dl - 0.23 gr/dl] (P=0.3926). This finding was in accordance with the results of paired t-test (p=0.3517). Reperfusion time non-significantly increased the predicted TP levels by 0.06 gr/dl [-0.23 gr/dl - 0.09 gr/dl] (P=0.3926), also in accordance with paired t-test (p=0.3172). However, erythropoietin administration and reperfusion time together produced a non-significant combined effect in decreasing the predicted TP levels by 0.03 gr/dl [-0.13 gr/dl - 0.06 gr/dl] (P=0.4430). Reviewing the above and Table 6-8 sum up concerning the alteration influence of Epo in connection with reperfusion time.

Discussion

A lot of clinical situations prove the association between TP levels and ischemic cases. Peng et al. [6] increased resistance to surgical stress by dietary preconditioning lacking essential nutrients in a mouse IR model injury. 6 to 14 days TP deprivation protected against renal and hepatic IR injury, resulting in preserved organ function. The amino acid starvation response and translational control is implicated in stress protection. Thus, short-term dietary interventions that modulate amino acid constitution can confer stress resistance in related IR models of surgical injury. Nayak et al. [7] suggested TP levels as a predictor for severity of acute ischemic stroke (AIS) patients since their significant changes were observed at different endpoints on and after admission, in discharged and more in patients on expired follow-up than matched healthy control ones. van der Hoeven et al. [8] associated the induced hemodynamic instability with the duration of brain death about the function of potential donor kidneys in Wistar rats and sham-operated controls. Organ function was studied by monitoring serum TP content. Progressive organ dysfunction and particularly kidney dysfunction was most pronounced in hemodynamically unstable brain-dead donors. When hemodynamic instability in the brain-dead donor was not corrected, kidney dysfunction was enhanced predisposing the graft for additional IR injury. Loehe et al. [9] subjected allotransplanted left lungs to 90 min warm IR before harvesting in non-heart-beating donors (NHBD) group, whereas lungs in HBD group were harvested immediately after cardiac arrest in native-bred pigs. After 24 h IR total period, the percentage of TP content, was significantly elevated in the bronchoalveolar lavage BAL fluid of NHBD group than sham-one. Sokolowski et al. [10] provoked already a decreased serum TP content in

DG	Difference	p-value
A-B	-0.13 gr/dl	0.2423
A-C	0.00 gr/dl	0.9900
A-D	0 gr	1.0000
B-C	0.13 gr/dl	0.2598
B-D	0.13 gr/dl	0.1011
C-D	-0.00 gr/dl	0.9883

Table 6: Statistical significance of mean values difference for groups (DG) after statistical paired t test application.

			P-Values	
Decrease	95% c. in.	Reperfusion	-test	glm
-0.03 gr/dl	-0.53 gr/dl	1 h	0.008	0.9027
-0.335 gr/dl	-0.70 gr/dl	1.5 h	0.0220	0.0719
-0.64 gr/dl	-1.17 gr/dl	2 h	0.0304	0.0226
± 0.175 gr/dl	-0.20 gr/dl	reperfusion time	0.2992	0.3547
0.2063637gr/dl	-0.42 gr/dl			0.0657

Table 7: The decreasing influence of erythropoietin in connection with reperfusion time.

Decrease	± SD	Reperfusion time	p-values
-0.02%	± 2.47%	1 h	0.9904
-1.27%	± 1.51%	1.5 h	0.3721
-2.52%	± 2.03%	2 h	0.1509
± 1.27%	± 1.51%	reperfusion time	0.3549
-0.68%	± 2.48%	interaction	0.4430

Table 8: The (%) decreasing influence of erythropoietin in connection with reperfusion time.

first 4-8 h of experimental acute pancreatitis in rats. Simmons et al. [11] indicated that the more caudal spinal cord segments suffer from slight but significant increase in vasogenic edema, the greater differential focal subsequent TP levels increase occurs during experimental autoimmune encephalomyelitis (EAE) in rat. Mrsulja et al. [12] found reduced TP levels after bilateral totally reversible common carotid IR arteries in gerbils.

Also, TP level is a factor influenced by Epo administration. Dame et al. [13] evaluated significantly higher the renal Epo and total protein excretion but same their ratio in preterm infants with gestational ages <29 weeks than more mature infants, reaching up to 23% of the administered high-dose rEpo (3 × 3,000 U/kg within 42 h after birth;) within 8 h after each infusion, possibly attributed to a higher glomerular filtration leakage due to lower kidneys maturation, considering potent neuroprotection of rEpo in very preterm and (near-) term neonates at high risk of hypoxic-ischemic brain injury encephalopathy. Małyszko et al. [14] studied the effects of 3-month Epo treatment in continuous ambulatory peritoneal dialysis (CAPD) patients and on CAPD control ones without rHuEPO and healthy volunteers ones. Borawski et al. [15] found that treatment with 4-weeks 2,000 IU rHuEpo therapy SC did not affect TP levels in patients receiving maintenance hemodialysis which activate vascular endothelium. Sezer et al. [16] observed a decrease in Epo dose and a significant improvement in nutritional status (TP levels) in patients altered from 6 months HD treatment program to 6 months CAPD one. Few references' clear claim that Epo administration results in a slight increasing effect on serum TP levels will be held, since our results (Tables 7 and 8) show a short-term slight non significant decrease on these. Perhaps a longer study time or a greater Epo dose may coincide with the references' claim, although Table 1 shows a noteworthy short-term restoration capacity of this certain Epo dose on alkaline phosphatase, CPK and LDH levels but a controversial one on white blood cells level. Nevertheless, a protective effect from the deviating injury on uric acid and sodium levels and conservative non significant effects on mean corpuscular hemoglobin, platelet distribution width and plateletcrit levels seem also on Table 1 [17-20].

Conclusion

Epo administration either alone or interacted with reperfusion time has non-significant short – term decreasing effects on blood TP levels. Perhaps, a longer study time or a higher Epo dose may reveal more significant results aligned with bibliography. This information must be into consideration upon laboratory investigation of neurologic diseases in case of being co-treated by Epo [21-26].

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