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Diisononyl Phthalate Perturbs Immune Cell Energy Transduction by Disrupting Some Splenic and Lymphocyte Energy Metabolising Enzymes Activities

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ABSTRACT

Background Energy homeostasis is a hallmark of cell survival and maintenance of cell function, some cell types (e.g., immune cells such as the spleen and lymphocyte) have special functions that demand energy over and above the basic rate (e.g., for antigen processing and presentation, migration and phagocytosis). Independently of the amount of energy needed by cells or the kind of nutrients they metabolize to generate energy, the immediate donor of free energy is mainly represented by adenosine-5'-triphosphate (ATP). The effect of diisononyl phthalate (DiNP) on splenic and lymphocyte energy metabolism was examined.

Methods: Eighteen Wistar rats were divided into 3 groups of six rats each: Group A received Tween-80 (control), DiNP (20 mg/kg/BW) was given to Group B, and 200mg/kg DiNP was given to Group C orally (gavage) for 14 days. The activity of splenic and lymphocyte glycolytic, tricarboxylic acid cycle and oxidative phosphorylation enzymes were assessed.

Results: The glycolytic, tricarboxylic acid cycle and oxidative phosphorylation enzymes studied were predominantly downregulated, except for splenic and lymphocyte lactate dehydrogenase activity at 20mg/kg DiNP relative to control ($P < 0.05$). DiNP exposure was found to impair splenic and lymphocyte energy transduction enzymes.

Conclusion: Our findings call the need for studying the key energy metabolism pathways and enzymes for diagnosis, disease activity monitoring, guidance for energy metabolism-targeted therapy and monitoring systemic inflammation.

Keywords: Energy Metabolism Targeted Therapy; Diisononyl Phthalate; Spleen; Lymphocyte; Glycolysis; Oxidative Phosphorylation

Abbreviations: DINP: Diisononyl Phthalate; PVC: Polyvinyl Chloride; DEHP: Di-2-Ethylhexyl Phthalate; NK: Natural Killer; EDTA: Ethylenediaminetetraacetic Acid; NADH: Nicotinamide Adenine Dinucleotide, ALD: Aldolase; LDH: Lactate Dehydrogenase; IDH: Isocitrate Dehydrogenase

Introduction

The most popular plasticizers are phthalates (PAEs), which are added to polyvinyl chloride (PVC) to increase flexibility. Phthalate molecules contaminate the atmosphere, foods, or bodily fluids, exposing both people and the environment they live in (Oje, et al. [1,2]). Phthalates have been frequently implicated in reproductive issues (Kehinde, et al. [2]), cardiac effects (Kehinde, et al. [3]), neurological problems, and carcinogenic effects, but reports linking them to some allergic conditions have drawn more attention to their immunotoxicology (Li, et al. [4,5]). Diisononyl phthalate (DINP) is a plasticizer that softens polyvinyl chloride (PVC) materials utilise in place of di-2-ethylhexyl phthalate (DEHP). Through eating, inhalation, and skin contact, humans are exposed to DINP. Over 90% of all DINP intake is thought to occur through ingestion, making it the primary route (Chen, et al. [6]). Immunomodulation is an important approach for raising the body's defences against a range of disorders. It means

that the immune system is being activated broadly and implies that the creation of effector molecules and the actions of macrophages, natural killer (NK) cells, granulocytes, complement, and lymphocytes are being stimulated without the need for an antigen (Dapas, et al. [7]). Spleen, a secondary lymphoid organ is involved in blood storage, the immunological monitoring of bloodborne antigens, and the eradication of old or aberrant blood cells. Additionally, the spleen shelters and aids in the maturation of immune system cells known as lymphocytes. White blood cells called lymphocytes offer defence against pathogens that have managed to infect body cells. By regulating diseased cells, lymphocytes also defend the body against malignant cells. The immune response to infections and antigens in the blood benefits from the spleen (MacIver, et al. [8]). T, B, and natural killer (NK) cells are examples of lymphocytes, which are white blood cells that have a uniform appearance but perform a variety of functions (La Motte-Mohs, et al [9]). In this study, the energy metabolism of the lymphocytes and spleen of rats exposed to DiNP was examined. This is the first investigation into how DiNP affects the splenic and lymphocyte glycolytic, tricarboxylic acid cycle, and oxidative phosphorylation enzymes in DiNP-treated rats.

Methods

Chemicals and Assay Kits

DiNP was purchased from Relonchem Ltd. (Cheshire, United Kingdom). Lactate dehydrogenase test kit was procured from CYPRESS® Diagnostics (Langdrop, Belgium). Mannitol, sorbitol, sucrose, glucose- 6-phosphate dehydrogenase, ethylenediaminetetraacetic acid (EDTA), nicotinamide adenine dinucleotide (NADH), fructose-1,6-bisphosphate, succinate, phosphoenolpyruvate, oxaloacetate, rotenone, and all other reagents used were of the purest analytical grade and purchased from Sigma- Aldrich (Missouri, USA).

Experimental Animals

At the animal house of the University of Ibadan College of Medicine in Ibadan, 18 male Wistar rats (8 weeks) weighing 200–220g were purchased. The rats were kept in plastic cages at the Ajayi Crowther University animal house for acclimation and treatment. Acclimatization was done for a period of 7 days and rats were allowed unlimited access to pelletized food and water.

Study Design

Three groups of six rats each were created from the rats: DiNP was prepared with ordinary saline and Tween-80 (1:1 v/v). The doses of 20 and 200 mg/kg/day of DiNP were chosen based on prior studies (Kehinde et al., 2022). Group A was given tween/saline as a control, Group B received DiNP (20 mg/kg/BW), and Group C received 200 mg/kg of DiNP. All administrations were carried out over a 14-day period via oral galvage. Tween 80 was utilised as a co-solvent, but it has no impact on the outcomes of the experiments.

Collection of Samples

Isolation of Spleen: Animals were euthanized after the last treatment, and the spleen was removed while the animals were under anaesthesia. The removed spleen was cleaned in 1.15% KCL (ice-cold), blotted, weighed, and then homogenised in 10% weight/volume of 0.1 M phosphate-buffered saline (PBS; pH 7.4; 12,000 x g for 10 minutes at 4°C). The supernatant was used for biochemical tests.

Isolation of Lymphocytes and Mitochondrial Fraction: Mitochondria were processed and extracted from the spleen of rats (Erika, et al. [10]). Soon after blood collection through cardiac puncture, an aliquot of blood was used to isolate lymphocytes by differential centrifugation using Ficoll paque (Jaatinen and Laine [11]) and samples were kept at 4°C until the assay was started.

Determination of Splenic and Lymphocyte Glycolytic Enzymes Activity: The Colowick method was used to determine the activity of hexokinase (Colowick [12]). According to published method by Sims and Blass (Sims and Blass [13]), the phosphofructokinase (PFK) activity was determined using the method of Sims and (Blass [13]). The method reported by (Jagannathan, et al. [14]) was used to measure the activity of aldolase (ALD). As recommended by the manufacturer, the LDH Kit was used to assay the lactate dehydrogenase (LDH) activity (CYPRESS). Tatsumo et al. method was followed to measure NADase activity (Tatsumo, et al. [15]).

Determination of Splenic and Lymphocytes Electron Transport Chain Enzymes: Citrate synthase activity was assessed using the spectrophotometric enzyme test methodology published by (Yu, et al. [16]). As previously described by (Romkina and Kiriukhin, [17]), the isocitrate dehydrogenase (IDH) activity was measured. Using the α-KGDH Kit and following the manufacturer's (BioVision Incorporated) instructions, the activity of α-KGDH was assessed. According to (Lopez-Calcagno, et al. [18]), MDH activity was assessed.

Determination of Splenic and Lymphocytes Electron Transport Chain Enzymes: According to (Medja, et al. [19]),

1. Complex I (NADH ubiquinone oxidoreductase),
2. Complex II (succinate ubiquinone oxidoreductase,
3. Complex III (cytochrome c oxidoreductase) and
4. Complex IV (Cytochrome C Oxidase) activities weas determined.

Total Protein Determination: The amount of total protein in spleen and lymphocytes was measured using the (Gornall, et al. [20]).

Statistical Analysis

Results are presented as mean ±SD. The level of homogeneity between the groups was assessed using analysis of variance (ANOVA). When there was heterogeneity, Tukey's test was employed to divide the groups. All analyses were performed using GraphPad Prism® version 8. P values lower than 0.05 were considered statistically significant.

Result

DiNP Perturbs Splenic and Lymphocyte Glycolytic Enzymes Activities: Table 1 displays how DiNP affected the rat spleen and lymphocyte glycolytic enzyme activity. The activities of splenic and lymphocyte HK, ALD, PFK, and NADase were significantly (P <0.05) decreased after DiNP (20 and 200mg/kg) administration compared to the control group. However, splenic and lymphocyte LDH activity was downregulated at 200mg/kg DiNP compared to 20mg/kg DiNP (54% and 67%, respectively), indicating that 20mg/kg DiNP considerably boosted splenic and lymphocyte LDH activity relative to the control group by 60% and 5.6%, respectively.

Table 1: Effect of DiNP on Splenic and Lymphocyte Glycolytic enzymes.

GROUPS	SP HK (μ/mg protein) $x10^{-3}$	SP ALD (μ/mg protein) $x1^{0-3}$	SP PFK (μ/mg protein) $x10^{-3}$	SP LDH (μ/mg protein) $x10^{-3}$	SP NADase (μ/mg protein) $x10^{-3}$	LYM HK (μ/mg protein) $x10^{-3}$	LYM ALD (μ/mg protein) $x10^{-3}$	LYM PFK (μ/mg protein) $x10^{-3}$	LYM LDH (μ/mg protein) $x10^{-3}$	LYM NADase (μ/mg protein) $x10^{-3}$
Control	16.13 ± 0.89	28.18 ± 0.59	14.63 ± 0.61	18.72 ± 4.45	2.29 ± 0.21	3.93 ± 0.54	26.48 ± 0.59	23.96 ± 1.79	251.61 ± 12.48	0.47 ± 0.02
DiN-P(20mg/kg)	12.52 ± 0.77*	19.95 ± 1.34*	13.72 ± 0.89*	30.65 ± 2.26*	1.60 ± 0.27*	0.57 ± 0.09*	18.45 ± 0.62*	20.13 ± 0.58*	266.02 ± 13.06*	0.64 ± 0.03*
DiN-P(200mg/kg)	7.69 ± 0.63**	17.28 ± 1.43**	9.40 ± 1.24**	14.38 ± 1.39**	1.26 ± 0.08**	0.22 ± 0.06**	12.61 ± 0.78**	14.22 ± 1.08**	90.78 ± 3.34**	0.55 ± 0.09**

Note: *Significantly different when compared with control (P < 0.05) **significantly different when compared with DiNP (20mg/kg) (P < 0.05). DiNP- Diisononyl phthalate, HK- Hexokinase, ALD- Aldolase, PFK- Phosphofructokinase, LDH- Lactate dehydrogenase, LYM- Lymphocyte, SP- Spleen.

DiNP Downregulates Splenic and Lymphocyte Tricarboxylic Acid Cycle Enzymes Activities: The impact of DiNP on the splenic and lymphocyte tricarboxylic acid cycle enzyme activities in the study animals is shown in Figure 1 (A–H). According to the findings, splenic and lymphocyte CS, IDH, -KDH, and MDH activities significantly decreased when compared to control (P < 0.05). Activities continued to decline after the DiNP dose was increased to 200mg/kg from 20mg/kg.

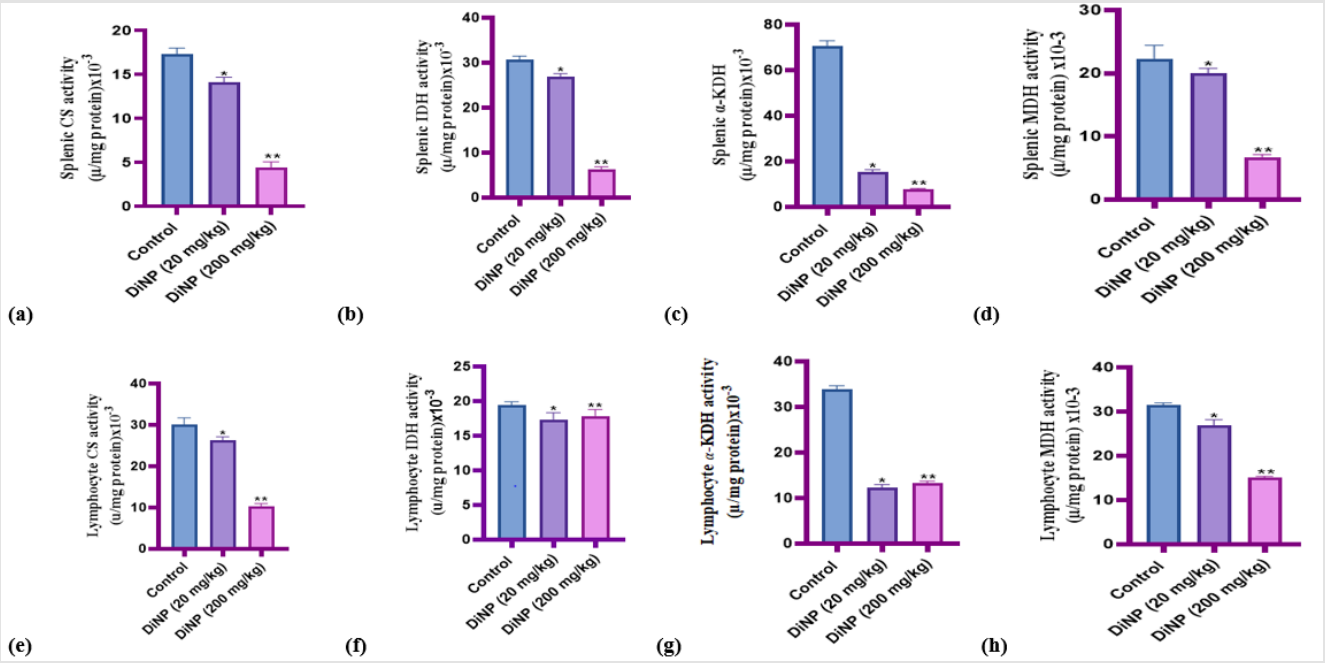

Figure 1: Effect of DiNP on splenic and lymphocyte tricarboxylic acid cycle enzymes activities in rats. The values are expressed as Mean ± SD of six rats (n = 6) in each group. *= significantly different from the control (P <0.05). **= Significantly different from the DiNP (20mg/kg) group (P <0.05). CS= citrate synthase, IDH= isocitrate dehydrogenase, α-KDH= alpha ketoglutarate dehydrogenase, MDH= malate dehydrogenase.

DiNP Downregulates Splenic and Lymphocyte Electron Transport Chain Enzymes Activities: Figure 2 (A-H) illustrates how DiNP affected the activity of splenic and lymphocyte electron transport chain enzymes in the study animals. According to the findings, splenic and lymphocyte CPLX I, CPLX II, CPLX III, and CPLX IV activity significantly decreased when compared to control ($P < 0.05$). At 200mg/kg DiNP dose, more downregulated activities were seen relative to the 20mg/kg.

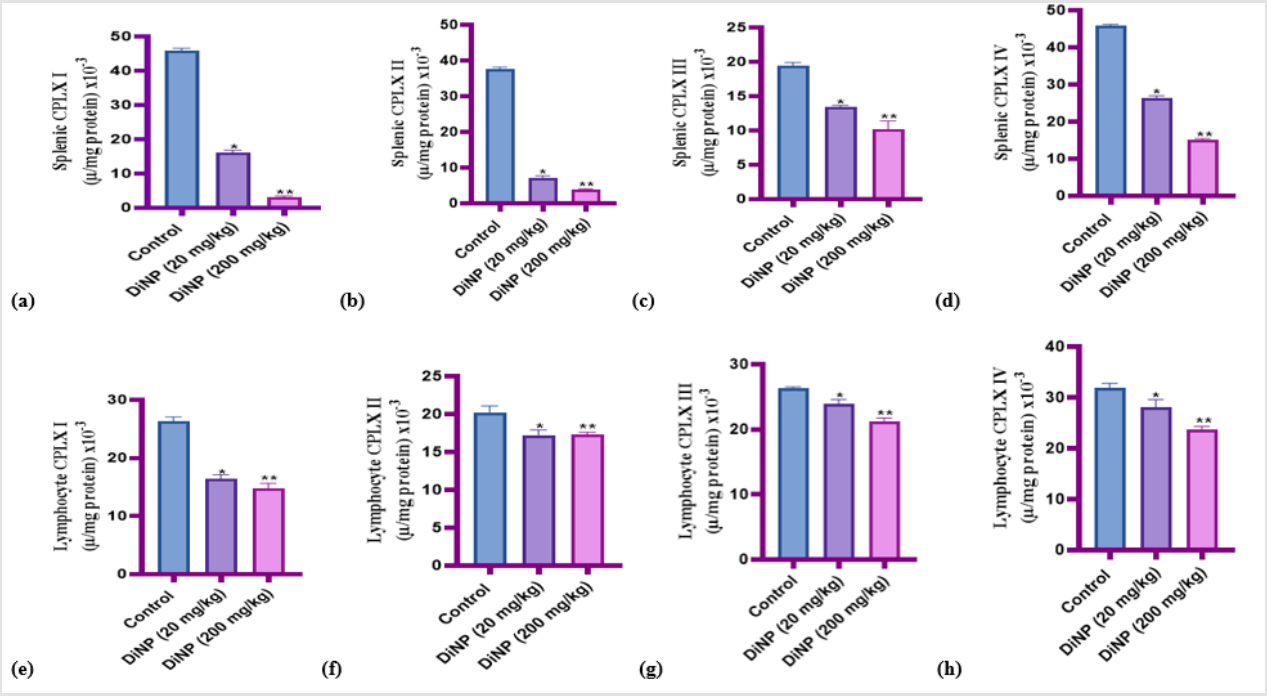

Figure 2: Effect of DiNP on splenic and lymphocyte electron transport chain enzymes activities in rats. The values are expressed as Mean ± SD of six rats (n = 6) in each group. *= significantly different from the control ($P < 0.05$). **= Significantly different from the DiNP (20mg/kg) group ($P < 0.05$). CPLX I= Complex I (NADH ubiquinone oxidoreductase), CPLX II= Complex II (succinate ubiquinone oxidoreductase), CPLX III= Complex III (cytochrome c oxidoreductase), CPLX IV= Complex IV (Cytochrome C Oxidase).

Discussion

Cell survival and maintenance of function are characterised by energy homeostasis, yet some cell types (such as immune cells) have specialised tasks that require energy above the basic rate (e.g., for antigen processing and presentation, migration and phagocytosis). Adenosine-5'-triphosphate (ATP) is the primary immediate provider of free energy, regardless of the amount of energy required by cells or the types of substances they metabolise to produce energy (Chaban, et al. [21]). This study uses rats as model and offers the first information regarding the spleen and lymphocyte's state of energy metabolism following exposure to DiNP. Because they have an impact on how the immune system reacts to pathogenic bacteria and other foreign substances, lymphocytes are recognised to play a crucial role in the immune system. T cells, B cells, and natural killer cells comprise lymphocytes (Berringto, et al. [22]). Different energy metabolism pathways are used by B and T cells depending on the circumstances. The lymph nodes and spleen, which are immune cells, typically function best in compartments with low oxygen (O_2) concentrations, or between 0.5 to 4.5% (Caldwell, et al. [23,24]). However, immune cells experience lower O_2 concentrations of 0.5–1.0% in pathophysiological circumstances, such as a location of acute and chronic tissue inflammation, which is brought on by an increased oxygen demand resulting from insufficient O_2 delivery (Gaber, et al. [25]). Lymphocytes are forced to travel against O_2 gradients by the hypoxic state mentioned above. Adenosine triphosphate (ATP), the main immediate supplier of energy for immune processes, comes from aerobic glycolysis and/or oxidative phosphorylation in the mitochondrial respiratory chain, both of which require O_2 (Buttgereit, et al. [26]). The T cells must rely on lipid oxidation and aerobic glycolysis in hypoxic conditions to meet their energy needs (Semenza [27]). Activated T cells and B cells have much higher levels of the glycolytic, pentose-phosphate, and glutaminolytic pathways (the glutaminolytic pathway provides a different supply of carbon for the TCA cycle, which converts glutamine to alpha ketoglutarate) (Pearce, et al. [28,29]). In this investigation, it was discovered that, with the exception of LDH activity, the activities of the glycolytic enzymes (HK, PFK, ALD, and NADase) were downregulated at both DiNP doses (20 mg/kg and 200 mg/kg) in comparison to the control group. This suggests that the glycolysis's final product, pyruvate, won't be available, and as a result, ATP production may be impeded. B cells (pro and pre) culture, as previously stated require py-

ruvate from glycolysis to fuel and maintain oxidative phosphorylation (OXPHOS), but the TCA substrates employed are unknown (Yin, et al. [30]). However, as compared to the control, the results of this study show that splenic and lymphocyte LDH activities were both elevated at 20mg/kg DiNP. Increased splenic and lymphocyte LDH activity suggests that lactate may be a substrate that feeds the TCA. Lactate is a key substrate for gluconeogenesis and enters the TCA via oxidation of pyruvate and then carboxylation of oxaloacetate. However, it was discovered that splenic and lymphocyte LDH activity was significantly lowered at 200 mg/kg DiNP. This finding shows that as DiNP concentration is raised, LDH activity may be hindered, making the alternative substrate for ATP synthesis unavailable. Furthermore, the enzymes of the succeeding pathways (TCA and OXPHOS) that should have cushioned the energy generation for the spleen and lymphocytes were blocked by the observed decreased splenic and lymphocyte glycolytic enzyme activities as a result of DiNP administration. T cells and dendritic cells are found in the spleen, where they interact to process antigens and are also directly exposed to cytokines that cause inflammation (Everts and Pearce [31]). Once activated, T cells' metabolism modifies, and during this increased energy requirement, aerobic glycolysis is utilised (Park and Pan [32-34]). For systemic inflammatory disease, monitoring spleen energy metabolism has been suggested to be a valuable technique for assessing disease activity and perhaps guiding energy metabolism-targeted therapy (Pak, et al. [35]). Inflammation and even impairment of some organs' energy homeostasis have both been linked to DiNP previously using murine models (Adeyemo, et al. 2022) (Ore, et al. [36-39]). As a result, the spleen and lymphocytes may have undergone inflammation, which would explain why the activity of the glycolytic, TCA, and OXPHOS enzymes have decreased.

Limitation of the Study

The lymphocyte employed for the investigation of energy metabolism was a limitation of this study because it was not differentiated into B or T cells. Using ficoll-paque, an isolated lymphocyte was produced from whole blood.

Conclusion

This research examined how DiNP (20 mg/kg and 200 mg/kg) affected the energy metabolism of lymphocytes and the spleen in rats. The spleen and lymphocytes' energy metabolism were found to be disturbed by DiNP. It was discovered that lactate serves as a substrate for the lymphocyte and spleen TCA cycle. The results of this study may point to important energy metabolism pathways that could be investigated for illness monitoring, diagnosis, energy metabolism-targeted therapy, and systemic inflammatory monitoring.

Author Contributions

Abosede Temitope Olajide; methodology: Abosede Temitope Olajide and Samuel Abiodun Kehinde; formal analysis, investigation, and resources: Abosede Temitope Olajide and Samuel Abiodun Kehinde; writing- original draft preparation, review and editing: Abosede Temitope Olajide and Samuel Abiodun Kehinde. The final manuscript has been reviewed and approved by the authors.

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Declaration of Interests

The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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