

Oxidative stress and diabetic nephropathy health and social care essay



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Title of assignment

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1 Introduction Diabetic nephropathy (DN) is the most serious complication in both type 1 and type 2 diabetes

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causing end-stage renal disease affecting ~40% of the patients¹⁻³.

Pathological features of DN are the thickening of the glomerular basement membrane, deposition of renal extracellular matrix, glomerular mesangial expansion and tubule-interstitial fibrosis⁴⁻⁷. These damage the glomerulus and is characterised based on the presence of micro albuminuria, macro albuminuria and decrease of the glomerular filtration rate⁷⁻¹⁰. The

progressive decline in glomerular function in the end, results in what is termed as end-stage renal disease. 1. 2 Hyperglycemia and Oxidative

stress Amongst other risk factors such as hypertension, smoking, dyslipidemia, hyperglycemia is the major risk factor. Hyperglycemia seems to be the major causal factor for the pathogenesis of DN¹⁰⁻¹⁴.

Hyperglycemia induces vascular complications through complex overlapping pathways: formation of advanced glycation end products (AGE), activation of protein kinase C (PKC), and generation of reactive oxygen species (ROS), among others^{1, 4, 5, 11, 15}. Hyperglycemic activation of these signal transduction cascades leads to an activation of genes causing a profibrotic environment and oxidative stress^{6, 9, 10, 15-17}. These lead to the

pathological features often seen with DN (fig. 1). 1. 3 Role of Reactive

Oxygen Species Previous publications have shown that Reactive Oxygen Species (ROS) plays an important role in the development and progression of DN^{1, 11, 13, 18}. In a state of hyperglycemia, there is an overproduction of ROS^{1, 8, 12, 14, 18}. ROS seems to be the mediator that causes

hyperglycemia induced vascular complications (fig. 1)^{1, 8, 12, 14, 18}. 1. 4

Aim Nicotinamide Adenine Dinucleotide Phosphate-Oxidase (NADPH Oxidase)

is the major source of the generation of ROS in non-phagocytic cells^{6, 16,}

17. ROS derived from the NADPH Oxidase isoform NOX 4 is thought to be the
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major contributor to the vascular complications observed in DN (fig. 1)1, 2, 4, 11. The aim of this report is to analyse two papers on NOX4 and deduce its role in oxidative stress and DN. Figure 12. 1 Article 1: Critical Role of Nox4-based NADPH Oxidase in glucose-induced oxidative stress in the kidney: Implications in type 2 Diabetic Nephropathy

In this study, the methodology was well crafted, the materials used were mentioned clearly and even their manufacturers' details were clearly stated. The sequence of the primers used for the measurement of NOX1, NOX 4 and GAPDH mRNA were stated. This paves the way for precise replication or supplementation of the same experiment. However its introduction was too focused on NOX4 itself and did not have details on how it affects the signalling pathways like the JNK and p38 map kinase, which are profibrotic and proinflammatory and also influential in the pathophysiology of DN. This study used db/db mice in comparison to control non-diabetic mice (db/m). Mouse proximal tubule cells (MPT) exposed to high glucose were also used to study hyperglycemia induced NOX4 derived ROS overproduction and its hyper activation of redox-sensitive signalling pathways. Both of which were good models of type 2 diabetes and have the ideal conditions necessary for testing the author's hypothesis. Results showed that expression of NOX4 appeared to be cortex specific when compared to control mice. H₂O₂, the ROS produced by NOX4 was significantly increased in the renal cortex as compared to control suggesting that NOX4 is responsible for the increase in ROS levels. There was an increase in NOX4's cell membrane partner p22phox and nox4 subunit p47phox. This suggests that these two units are possibly influential in the regulation of NOX4 activity and could be possible sites for therapeutic interventions. However, the expression of NOX2 was found to be decreased, <https://assignbuster.com/oxidative-stress-and-diabetic-nephropathy-health-and-social-care-essay/>

suggesting that NOX2 could counter regulate the up regulation of NOX4 via its down regulation however, further analysis needs to be done on this to confirm this plausible correlation/association as this was not done in this study. The upregulation of profibrotic and proinflammatory signalling pathways in db/db mice such as p38 map kinase suggests and the subsequent increase in TGF- β and fibronectin suggests that NOX4 upregulation is associated with the activation of the p38 map kinase pathway causing an increase in TGF- β and fibronectin^{6, 7}. This indicates another possible site of intervention to prevent the onset of fibrosis and inflammation in the kidney. The exposure of MPT cells to high glucose showed similar results as with db/db mice and further analysis by inhibiting NOX4 activity showed; 1) high glucose (D-glucose) NOX4 and ROS production 2) increase in p38 map kinase was observed 3) inhibition of NOX4 activity via GKT-136901 and siRNA markedly reduced ROS production and p38 map kinase^{7, 11, 13, 14, 16, 19}. Data from this study suggests NOX4 derived ROS promotes p38 map kinase activity causing the up regulation of TGF- β and fibronectin leading to renal inflammation and fibrosis.

2. 2 Article 2: Role of NOX4 in murine models of kidney disease
The aim of the study was to define the role of NOX4 in renal disease in vivo. The author's hypothesis was that NOX4 may not be important to the pathophysiology of renal disease. Results from the study supported the author's hypothesis and suggests that NOX4 may not be a major driver/contributor of renal disease. The data from this study does not support previous publications on NOX4 which have linked NOX4 to ROS and fibrosis in DN. Three experimental animal models of renal injury were used: streptozotocin induced diabetes 1, unilateral urethral obstruction (uuo) and 5/6 nephrectomy were studied in NOX4 inducible or <https://assignbuster.com/oxidative-stress-and-diabetic-nephropathy-health-and-social-care-essay/>

knockout mice in comparison with wild type mice. The animal models used were sufficient/appropriate to provide definitive evidence attesting the hypothesis mentioned by the author, although models of type 2 diabetes, db/db mice and ob/ob mice could have also been used¹². The author's findings were able to define NOX4's role in DN pathology. The data argued against previous publications' findings which suggest that NOX4 is a disease promoter. Instead, the author's findings found NOX4 to have a small, limited protective effect to inflammation, albuminuria and fibrosis. This suggests that NOX4 could be a protective enzyme rather than disease promoting. However, although the study was able to characterise the function of NOX4 in renal pathology, it was not able to prove the normal physiological function of NOX4. Further analysis should be in normal wild type mice to prove the normal physiological response of NOX4 although, having said that it is still a challenge to try and characterise the exact mechanisms upon which NOX4 acts on during normal cellular responses. The study was also unable to answer how NOX4 leads to a limited yet significant protective effect towards DN. Although it is true that their study was not designed to handle such a question but in their discussion they could have stated possible ways to further analyse and explore what they had just found out in this study. Instead it was only recommended that further studies should be cautious about translating cell culture and cell lines to the in vivo studies. Further exploration of the role of NOX4 in other experimental animal models or the study of the effects of NOX4 on other parts of the kidney apart from the tubules could help strengthen the author's conclusions and also further develop the knowledge on the physiological role of NOX4 and also aid in the pathophysiology and providing possible treatment options for DN. This study <https://assignbuster.com/oxidative-stress-and-diabetic-nephropathy-health-and-social-care-essay/>

did not take into consideration the p38 map kinase pathway which was thought to be activated by NOX4 derived ROS. Further studies should explore this using the animal models used by the author and further explore if NOX4 truly has a protective effect based on its actions on the p38 map kinase signalling pathway.

2.3 Comparison of Both Articles

Both studies to a certain extent complement each other in their findings. They both showed that NOX4 is highly expressed in kidney cells as compared to other homologs. They both suggest a normal physiological role for NOX4 although exact function remains unclear. Both articles used statistical tools such as one way anova and t-tests (paired or unpaired). Differences were significant if $p \text{ value} < 0.05$. Both studies used roughly the same concept for the design in their methodology. The same method was used to detect key proteins in the experiment. Western blotting was one of the main methods used. Article 1 used lucigenin-derived chemiluminescence assay to determine NADPH oxidase activity whereas article 2 used the immunostaining method instead. In article 1, each western blot analysis was accompanied by a graph which made it easier to visualise portray to target audience the significant differences. However in the article 2, not all western blot analysis was accompanied with a graph. This prevents a person from being able to clearly differentiate the significance between two variables. i. e., the bands of the western blot look similar in black and white and it is hard to differentiate the molecular weight clearly without a corresponding graph to rely on. A major area of contradiction was the role of NOX4 in DN. Article 1 suggested NOX4 to be a disease promoter through the overproduction of ROS leading to the activation of map kinase and the profibrotic signalling pathway. Article 2 suggested that NOX4 to have a limited protective effect on inflammation, <https://assignbuster.com/oxidative-stress-and-diabetic-nephropathy-health-and-social-care-essay/>

albuminuria and fibrosis. Article 1 through the inhibition of map kinases were able to block the production and activation of TGF- β indicating that map kinases is upstream of TGF- β . In article 2, data suggests that fibrosis was taking place independently and not through NOX4-derived ROS activated map kinases, in fact the data showed that NOX4 was protecting against inflammation and fibrosis and the stimuli thought to induce inflammation and fibrosis was also causing a reduction in NOX4 expression. Another area of contradiction was the role of the other NOX homologs; article 1 was able to suggest through its findings that NOX2 could counter regulate the up regulation of NOX4 via its down regulation suggesting a compensatory mechanism between the NOX homologs. However in article 2 no such findings were observed, instead expression of NOX1 and NOX2 remained similar to control and a decrease of NOX4 protein expression was observed in diabetic mice suggesting that NOX4 could be a marker for healthy cells rather than a disease promoter. It was also noted that in article 1, findings in mice models were similar to findings in the MPT cell lines. Article 2 suggested cell culture and cell lines could differ from in vivo analysis. Further studies should look into this as this could be true as sometimes the transport of certain proteins could be affected in vivo and may not end being transported to certain areas of the kidney. A limitation in both studies involves the use of mice kidneys. There is always a level of uncertainty weather the findings would be applicable to humans. However, the animal studies still do provide valuable insights into the pathophysiology of the disease and allow the exploration for possible interventions to reduce ROS and decrease oxidative stress and attenuate the progress or if not cure DN.

3. 1 Conclusion In conclusion, the role of NADPH Oxidase NOX4 in the <https://assignbuster.com/oxidative-stress-and-diabetic-nephropathy-health-and-social-care-essay/>

pathogenesis of DN was analysed. Although both articles had conflicting views on the role of the NOX4 in DN, it seems clear that the regulation of NOX4 seems to be the key factor that could provide a therapeutic option for the prevention of DN. Whether or not NOX4 is involved in inflammation and fibrosis and the major source of ROS causing DN still remains unclear. Further studies are required to examine and identify the exact mechanism by which NOX4 is linked to the pathogenesis of DN.