Institut für Diabetes » Gerhardt Katsch « Karlsbug
Direktor: Dr. Echard Salzsieder

OPINION

On the Dissertation of Shaybek Altynay Shuparovna
"Prevention by restored form of glutathione of the destruction of pancreatic B-cells caused by diabetogenic zinc binding chemicals and investigation of the mechanisms of its preventive activity" submitted for the scientific degree Doctor of Philosophy (PhD),
Speciality: 6D060700- Biology

Diabetes mellitus presents a serious global health problem. The population with diabetes worldwide was estimated to increase up to 693 million by 2045. One o f the most serious complications o f diabetes is cardiovascular disease and there are close associations between cardiovascular mortality and ill controlled hyperglycemia. As in other developed countries, cardiovascular disease is the main cause of death in Kazakhstan, it is thus an urgent problem to prevent metabolic disorders, organ damage, and premature death due to diabetes complications. Disturbances in carbohydrate metabolism, as they occur in diabetes, have multiple causes. The mechanism how they are induced and the various pathological outcomes are not yet fully understood. However, the progressive deterioration o f the function and destruction o f insulin-producing pancreatic β-cells play a key role in the onset of diabetes mellitus.Thus, the β-cells are in the focus o f current research, providing a clue for new therapies that may preserve the insulin secretory capacity.

To explore the m echanisms of β-cell dysfunction, it is therefore o f utmost importance to investigate pathological changes in the β-cells o f the pancreas that may be caused by potentially diabetogenic agents. In this respect, zinc is an integral part o f pancreatic β-cells with zinc concentrations reaching 10 - 20 mmol/L in the interior of the dense-core granule. Zinc ions are

essential for healthy β-cells and are essential for correct processing, storage, and secretion of insulin. Studies have shown that reducing granule zinc with various zinc-binding agents, i.e. chelators, do induce diabetes in some animal models.
Consequently, the doctoral candidate has focused in her thesis on these aspects using experimental animals and the model of cultured pancreatic islets to study the mechanism of action by which deleterious effects o f zinc-binding agents, such as dithizone and 8-hydroxychinoline, on the β-cells can be prevented. For this purpose, the naturally occurring tripeptide glutathione has been used.

Comparison o f the protective potential of reduced glutathione and oxidized glutathione against diabetogenic zinc-chelating agents is a demanding goal. The approach of identifying mechanisms that can prevent damage of the β-cells using glutathione, displays originality.
Whereas the tripeptide glutathione is a natural constituent of cells, chemical agents capable of binding zinc in β-cells have several adverse effects and are thus notsuitable to study mechanisms of physiological relevance. The methods used for the investigation were adequate to achieve the aim of the study and correspond to international standards. It should be emphasized that the methods developed andapplied in the present study are demanding and not many research groups throughout the world are able to do such sophisticated studies. Especially, the good quality of the immunohistochemical stainings deserves emphasis. Furthermore, the candidate has combined biochemical methods and histological/immunohistochemical measures to investigate the pathophysiological/histopatholgical changes that occur in the β-cells, and the stainings were quantitatively evaluated. The results clearly show for the first time that reduced glutathione, but not its oxidized form, can prevent depletion of zinc from the β-cells. Likewise cysteine, is a protector. This is a very important approach for the development o f new antidiabetic drugs to preserve residual β-cell function in patients with type 2 diabetes.
The candidate performed an excellent experimental work and contributed to the elucidation of the pathology of the β-cell.

In summary, the work was carefully done and has provided new results and insight into the m echanisms of β-cell protection not previously described in the literature. The dissertation project had already produced articles that were recently published in peer-reviewed journals and

results were presented at international congresses. Moreover, an extensive literature review was performed. I agree with the can d id ate's conclusion that glutathione protects the β-cells against diabetogenic agents, and increasing intracellular glutathione should be considered to reduce the risk of developing diabetes mellitus.

Taken together the outcom e of this thesis is a valuable contribution to the field of international clinical diabetes research. It is for this reason that 1 strongly recommend acceptance of this doctoral thesis by the Scientific Committee.

In the reviewer's opinion, the candidate Shaybek Altynay Shuparovna has fulfilled the required criteria for the scientific degree “Doctor of Philosophy (PhD)”speciality Biology 6D060700.

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