

Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2020)

Date: 2021/4/12

To Director of Institute for Molecular and Cellular Regulation, Gunma University

Principal Applicant	
Institution	Endocrinology department, Beijing Tongren Hospital, Capital Medical University
Position	Professor and Director
Name	Jinkui Yang

We report on the results of joint research in fiscal 2020 as below.

(Program No.19003)

1. Research Title	Berberine improves insulin secretion through hERG2 potassium channel				
2. Purpose and Significance of the research project	Coptis Chinensis is an ancient Chinese herb treating diabetes in China for thousands of years. However, its underlying mechanism remains poorly understood. Here, we report the effects of its main active component, berberine (BBR), in stimulating insulin secretion in a high glucose-dependent manner. In mice with hyperglycemia induced by high-fat diet, BBR significantly increased blood insulin and reduced blood glucose. However, in mice with hyperglycemia induced by Kcnh6 global or pancreatic islet β -cell-specific knockout, BBR exhibited no beneficial effects. BBR reduced KCNH6 voltage-dependent K ⁺ (Kv) currents. This reduction was caused by disturbing KCNH6 channel distribution on the plasma membrane, resulting in prolongation of high glucose-induced cell membrane depolarization. Consequently, BBR enhanced high glucose-dependent insulin secretion. Finally, a phase 1 clinical trial confirmed high glucose-dependent effect of BBR on insulin secretion. These findings suggest that BBR is a new glucose-dependent insulin secretagogue for the treatment of diabetes without causing hypoglycemia.				
3. Period of The Program	April 1, 2020 ~ March 31, 2021				
4. Project Members					
Name	Age	Gender	Institution/Department	Position	Role
(Principal Applicant) Jin-kui Yang	58	M	Endocrinology department, Beijing Tongren Hospital, Capital Medical University	Professor	Project director
(Research Collaborators) Jing Lu	40	F	Endocrinology lab, Beijing Tongren Hospital, Capital Medical University	Associate professor	Experimental executor
Miao-miao Zhao	27	F	Endocrinology department, Beijing Tongren Hospital, Capital Medical University	Graduate student	Experimental executor



Hao Wang	39	M	Molecular endocrinology and metabolism, IMCR, Gunma University	Assistant professor	Experimental executor
※If additional space is required, attach a separate sheet.					
5. Collaborative Researcher of IMCR	Name of the Laboratory	Molecular Endocrinology and Metabolism	Name	Tetsuro Izumi	

6. Research Plans

1. Isolation of cell fractionation: Cell fractionation will be isolated from pancreatic β -cells to detect the expression of KCNH6 using specific antibody as the marker of different subcellular organelles and plasma membrane.
2. Confocal microscopy (Immunofluorescence): To check localization of KCNH6 in pancreatic β -cells by using immunostaining with KCNH6 and different specific antibody as the marker of different subcellular organelles and plasma membrane.
3. TIRF microscopy: The dynamic trafficking process of KCNH6 under different stimulation (e.g. high glucose, high glucose plus BBR) will be observed by TIRF microscope.

7. Research results:

- 1) BBR can regulate the function of hERG2 potassium channel in pancreatic beta cells. Longer incubation but not short incubation of BBR would cause higher expression level of hERG2 on plasma membrane of pancreatic beta cells.
- 2) BBR promoted insulin exocytosis through mediating hERG2 potassium channel.

8. Publications and/or Presentations resulting from Joint Research Program with IMCR.
Exchange of information on joint research with faculty members.

① Please describe a list of publications in which the name of the collaborative researcher of IMCR appears and send one paper reprints of each publication to IMCR.

Not yet.

This project is now under review of Journal of Nature Communication.

② Please describe a list of publications which include the description that the research is supported by Joint Research Program with IMCR and send one copy of each publication to IMCR.

Not yet.

③ Enter the name of the conference, the date of the conference, and the title of the presentation of the conference. (up to 3 cases)

1. Jinkui Yang, Biomarkers of Diabetes and its Complications. The 2nd IMCR Symposium on Endocrine and Metabolism, 10th-11th November, 2016, Maebashi, Japan
2. Izumi Tetsuro, Insulin Regulates Lipolysis and Fat Mass by Upregulating Growth-Differentiation Factor 3 in Adipose Tissue Macrophages. The 1st Annual conference of Beijing Diabetes Institute, 30th Jan-2nd Feb, 2018, Beijing, China.
3. Izumi Tetsuro, Melanophilin Accelerates Insulin Granule Fusion without Predocking to the Plasma Membrane. The 2nd Annual conference of Beijing Diabetes Institute, 27th-30th June, 2019, Beijing, China.

④ Implementation status of information exchange with faculty members in charge of joint research.

We always communicated with Professor Izumi and Assistant Professor Wang for our joint research program.