THE RECEPTOR

Message from the Chair
Hubert Vesper, PhD,
Centers for Disease Control and Prevention

Dear Endocrinology Division Members,

The AACC introduced new tools and made some changes to its governance structure to allow division members to communicate more effectively and to have the division members more actively involved in scientific and programmatic activities: “The Artery” is a new tool for quick and easy communication among division members, for posting questions or sharing information. I would like to encourage everyone to visit our Endocrinology Forum and to take advantage of this new, free service. In this context, I would like to introduce and welcome our new moderator for “The Artery”: Dr. Amy Pyle-Eilola is from Nationwide Children’s and will take over for Dr. Stanley Lo on May 1st.

The new AACC Science & Practice Core Committee will be composed of the chairs of each of the divisions (or their designees) and will provide advice to the AACC Board of Directors regarding new issues in laboratory medicine which the AACC should address. This is a major change in the governance structure that gives our division and you the opportunity to more directly interact with the board. Further details are provided in below by Dr. Faix, one of the architects of this new structure.

Focusing in on our division, this year we will have our first elections for two officers: treasurer and nominating committee member. I would like to thank Jim Faix and Larry Demers for their help with identifying new candidates. Notifications for the elections will be sent to you soon. Stay tuned.

This year, we had two brief surveys and I would like to thank everyone for participating. The survey on “Standardized Reference Intervals for Thyroid Testing” is still open for participation. Further information about this survey is provided by Dr. Linda Thienpont in this letter. We will share the results from both surveys in the next newsletter and will discuss them at our division meeting at the annual AACC meeting. This brings me to my last item:

Please mark your calendar for our division meeting on Monday, August 1st, 2016, from 12 noon to 2 pm at the Marriott Hotel (connected to the convention center).
Like last year, we will have presentations and plan on providing educational credits for attending this event. Also, given the great success of last year’s poster walk, we will continue to have poster walks this year. They will be held on Tuesday, August 2nd and Wednesday August 3rd 2015. In addition, we will award the best abstracts. Thus, I would like to encourage you to submit the great work you are doing!

With best regards,

Hubert

New Role for the Endocrinology Division

There is a new governance structure proposed for the AACC which will place the divisions closer to the heart of the organization. Existing committees have been reorganized and there will now be five "core" committees drawing on the talents and expertise of the general membership reporting directly to the Board of Directors (see figure below).

The Science & Practice Core Committee will guide AACC’s activities in research, science and the translation of science into clinical practice. It will be composed of the chairs of each of the divisions (or their designees). This means that the divisions will be
more actively involved in the development of practice documents and scientific statements, the development of AACC programming (including at the Annual Meeting) and advising the Board regarding new issues in laboratory medicine which the AACC should address. All AACC members will be hearing more about this new proposed governance structure (and some of the changes will require a vote of the general membership) but the leadership of the Endocrinology Division wanted to share this news with its members. Do you have any ideas or suggestions about endocrine-related topics which the new committee should address?

Thyroid Function Tests – We Need Your Help!

Linda M Thienpont, Jim Faix, Graham Beastall

All members of the AACC Endocrinology Division know that the identification of subclinical thyroid disease depends on testing for TSH and free thyroxine (FT4). They probably also suspect that results for both analytes vary considerably when using different commercially available assays. There is no doubt that standardization of TSH and FT4 assays would improve patient care.

Several years ago, the IFCC formed a working group to examine this problem. Today there is a full-fledged committee devoted to the standardization of thyroid function tests (C-STFT). We have worked hard to define what we need to measure, develop reference measurement procedures (RMPs), examine the degree of variability currently existing in commercially available assays, and propose a path forward to standardization. For FT4, we proposed equilibrium dialysis (ED) combined with isotope dilution-tandem mass spectrometry (ID/MSMS), an RMP developed and validated by Ghent University. Developing a reference measurement system for TSH was not as straightforward, for a number of reasons. Therefore, the C-STFT proposed “harmonization” rather than standardization for TSH measurement, based on a panel of samples with values assigned using the all-procedure trimmed mean (APTM).

Twelve manufacturers are currently on board. They are (in alphabetical order) Abbott, Beckman Coulter, BioMérieux, Diasorin, Fujirebio, Maccura, Mindray, Ortho Clinical Diagnostics, Roche, Siemens, Snibe and TOSOH. Each company has conducted several method comparison studies for both FT4 and TSH using clinical specimens representing the complete spectrum of thyroid disease. The results of these studies show that most FT4 assays have a huge negative bias compared to ED/ID/MSMS. Although many TSH assays deviate from the APTM, TSH assays overall seem to agree reasonably well. The studies further demonstrated that recalibration against the RMP or APTM targets is able to significantly eliminate the observed deviations (compare the plots in the figure below).
At the request of our industry partners, the C-STFT contacted the FDA and shared our plans for eventual harmonization of TSH and standardization of FT4. The response was positive but the FDA emphasized the need to reach out to stakeholders and elicit opinions regarding the risks as well as the benefits associated with moving forward. As experts in laboratory endocrinology, you are an important group of stakeholders. We need your input to help answer the following questions.

Do you think it would be a benefit if all FT4 and TSH assays gave comparable results? What risks to patient safety do you think may arise as a consequence of a change in the numerical results for patients with thyroid disorders who are being followed (despite the appropriate similar change in the reference intervals)? And, perhaps most importantly, what measures would your laboratory take to minimize these risks?

This call has been launched in parallel to several clinical journals, to professional organizations for doctors, and patients in Europe, USA and Japan. The views of all
stakeholders will help the C-STFT and its industry partners determine the best way to propose agree global implementation. Please complete the survey we launched and/or contact any or all of us and let us know your thoughts.

Linda M. Thienpont PhD (linda.thienpont@ugent.be) is Prof. Emeritus from Ghent University, Belgium and chair of the IFCC C-STFT. Jim Faix, MD (jfaix@montefiore.org) is Director of Clinical Chemistry and Immunology at Montefiore Medical Center and a member of the committee. Graham Beastall PhD (gbeastall@googlemail.com) is Past President at International Federation of Clinical Chemistry & Laboratory Medicine.

Opinions in Endocrinology

Glucokinase activators as new therapeutic interventions for type 2 diabetes mellitus

William E. Winter, MD

As persons interested in the endocrine system, we are also interested in the treatment of endocrine disorders. The treatment of type 2 diabetes mellitus (T2DM) has moved from the simple (?) days of diet, exercise, weight loss, and sulfonylureas and/or metformin or insulin to a dazzling array of therapeutic agents. For example, drugs that increase incretin activity include [1] glucagon-like peptide-1 (GLP-1) agonists (e.g., exenatide) and [2] drugs that inhibit the metabolism of incretins via the inhibition of dipeptylprotease-4 (DPP-4) (e.g., sitagliptin). As another example, amylin reduces hepatic glucose production, slows gastric emptying and reduces glucagon levels. Inhibitors of the sodium-linked glucose transporter-2 [SGLT-2; encoded by SLC5A2, solute carrier family 5 (sodium/glucose cotransporter), member 2] (e.g., canagliflozin) impair urinary glucose reabsorption causing glycosuria that reduces plasma glucose.

To understand the newest family of drugs undergoing current trials, the glucokinase activators (GKA), we need to “examine” glucose metabolism and the beta cell. After glucose absorption from the gut, glucose circulates systemically and, by diffusion, enters into the interstitium. The beta cell secretes insulin that binds to insulin receptors on insulin responsive tissues: liver, skeletal muscle and fat (Figure 1). Uptake of glucose by these tissues lowers the plasma glucose concentration that had risen following a meal. Thus glucose homeostasis is maintained.
In terms of the beta cell (Figure 2), glucose enters the cytoplasm via the facilitative glucose transporter GLUT2 that is encoded by *SLC2A2* [solute carrier family 2 (facilitated glucose transporter), member 2]. Glucose is then phosphorylated to glucose-6-phosphate (G6P) by glucose kinase (GK; a.k.a. – hexokinase 4). Compared to other hexokinases, GK has a higher Km for the conversion of glucose to G6P. Over the physiological range of glucose concentrations, the rate of formation of G6P is dependent on the extracellular glucose concentration. As extracellular glucose concentrations rise, normally the rate of formation of G6P increases. In this way GK is the “glucose sensor” of the beta cell. With aerobic metabolism and the action of the mitochondria where oxidative phosphorylation and electron transport take place, G6P then yields high levels of ATP (~38 ATPs for each glucose molecule that is burned). This is approximately 20 times as efficient as anaerobic glycolysis that only yields 2 molecules of ATP per glucose molecule burned.
ATP subsequently binds to the beta cell’s sulfonylurea receptor 1 (SUR1) that is encoded by \textit{ABCC8} [ATP-binding cassette, sub-family C (CFTR/MRP), member 8]. Four SUR1 molecules surround four \textit{Kir} 6.2 molecules [encoded by \textit{KCNJ8}; potassium channel, inwardly rectifying subfamily J, member 8] that constitute a beta-cell potassium channel that is inwardly rectified. With ATP binding, this potassium channel closes, the beta cell depolarizes and a voltage-gated L-type Ca\textsuperscript{2+}-channel opens. Entry of calcium into the cytoplasm of the beta cell triggers insulin release. Other factors that stimulate insulin release include the incretins (as mentioned about) and fatty acids that are perceived by GPR40 that is encoded by \textit{FFAR1} (free fatty acid receptor 1).

GK is expressed in hepatocytes in addition to beta cells (Figure 3). Insulin regulates hepatocyte GK expression. In the hepatocytes, the action of GK is similar to the action of GK in beta cells: the conversion of glucose to G6P. Because insulin regulates hepatocyte GK expression, the liver is somewhat of a “slave” to the beta cell.
Clinical trials are in progress exploring a new class of antidiabetic drugs that activate GK which is the beta cell’s glucose sensor. Small-molecule glucokinase activators (GKAs) that stimulate the beta cell’s GK have displayed the following limitations: [1] lack of durable action (e.g., after 1 or more months glucose levels rise), [2] an increased frequency of hypertriglyceridemia and [3] an increased frequency of hypertension. To address these issues, a novel GKA named TTP399 was developed that selectively activates the hepatic GK. This drug is currently undergoing a phase 2 trial (see: https://clinicaltrials.gov/ct2/show/record/NCT02405260?term=TTP399&rank=1).

We will “stay tuned” to see whether this liver-selective GK activator proves to be more beneficial than the beta-cell GKAs. As well, if GKA are indeed efficacious, it will be interesting to see where these drugs fit into the growing pharmaceutical armamentarium that is combating T2DM.

References of interest:


Roma LP, Duprez J, Jonas JC. Glucokinase activation is beneficial or toxic to cultured rat pancreatic islets depending on the prevailing glucose concentration. Am J Physiol Endocrinol Metab. 2015 Oct 1;309(7):E632-9.
