Terahertz spectroscopy for diabetes diagnostics

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Introduction

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the produced insulin. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves. The development of diabetes mellitus leads to violation of carbohydrate, protein, and lipid exchange and is accompanied by a significant increase in the content of glucose, corticosteroid hormones, and some other metabolites in blood. The development of new rapid diagnostic methods for diabetes and its complications is an urgent problem.

Terahertz (THz) radiation has a number of useful features for medical applications. It is sensitive to water concentration and state, it does not ionize biological objects [1] and passes through the skin [2]. A distinctive feature of THz time domain spectroscopy is the possibility of measuring directly the refractive index and absorption coefficient, and hence complex permittivity spectrum of the sample in a single scan and in a broad frequency range [3]. This circumstance makes it possible to obtain a detailed spectral characteristic of a sample during one measurement, due to which rapid and even remote diagnostics is foreseen.

Experimental

Our THz time-domain apparatus was described previously [4, 5]. We used the radiation of a Ti:sapphire laser with a wavelength of 790 nm, a pulse duration of 90 fs with 1 Wt average power. For THz emission, the semiconductor (LT-GaAs) surface was illuminated by laser beam. For THz detection the electro-optical ZnTe crystal of 1 mm thickness was probed by a small, delayed fraction of laser beam. We have used both transmission (for blood plasma) and attenuated total internal reflection (ATR) configurations (for blood plasma and skin). The spectral range of reliable measurements was between 0.05 and 3.2 THz. We analyzed blood plasma of a rat with experimental diabetes. In additional the ATR spectra of human skin on the palm of the hand in vivo were measured at a normal blood glucose concentration (4.2–5.9 mM) and 45 and 90 minutes later after drinking the glucose solution (75 g per 100 ml of water). This is the standard oral glucose tolerance test, which demonstrates an initial spike and rapidly returns to normal levels of blood glucose concentration.

Results

THz spectroscopy of biological samples mainly probes water strong absorption and dispersion in THz ranges. It is known that relaxation time of water molecules involved in hydration of biomolecules are different from those of characterizing free, unbound water molecules, which is reflected in the low-frequency absorption and refraction spectra of biological samples (tissues, blood plasma) [4]. We have previously shown the insertion of glucose into water leads only to an increase of relaxation time τ_1 of the slow Debye process of this solution. The increasing of protein albumin concentration in the solution results in a decrease of the amplitude $\Delta\varepsilon_1$ of the slow Debye relaxation process [5]. This explains observed sensitivity of THz skin reflection spectra and blood plasma properties.

The figure 1 a) shows the averaged absorption coefficient difference for healthy and rat with alloxane diabetes. That is the difference between distilled water and studied solution.

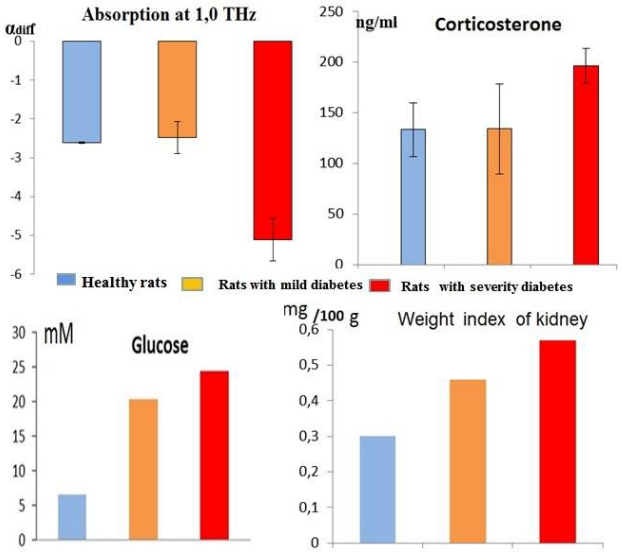

Fig. 1. The absorption coefficient differences at 1 THz, corticosterone and glucose concentration in blood plasma, and weight index of kidney of healthy (blue), mild diabetics (orange) and severity diabetics (red) rats

The absorption coefficient differs in group of rats with severity diabetes by a factor of more than two from the corresponding value in other groups. This fact indicates that some components secreted into the blood plasma under experimental diabetes complications may contribute to the total absorption. The rats with severity diabetes differed by a reliably high level of corticosteroid hormones in blood and adrenal glands, a large weight index of kidney, and a higher level of glucose in blood in comparison with the healthy and mild diabetics rats [6]. The decrease in the amplitudes of absorption spectra of blood plasma of rats with severity diabetes can be consid-

ered as an integral estimate of significant biochemical disturbances in Diabetes.

Assuming that the observed spectral changes are due to changes in the state of water in blood plasma, we have selected one of the parameters of the Debye model aqueous solution – $\Delta\varepsilon_1/\tau_1$, leading to the spectral features observed in the experiment. This change in the response of bound water can be the reason of the observed changes in our experiments at increasing glucose concentration in blood. We have demonstrated that when the concentration of glucose in blood rises to 24 mM (in rats with severity diabetes), $\Delta\varepsilon_1/\tau_D$ ratio decreases 1.2 times.

The correlation of the ATR amplitude of human skin and glucose concentration in blood is demonstrated in figure 2. In this case we use ATR amplitude R_{int} integrated over the used frequency range, and time shift ΔT [7]. It can be seen that the variations of the optical characteristics of human skin correlate with the changes in blood glucose level.

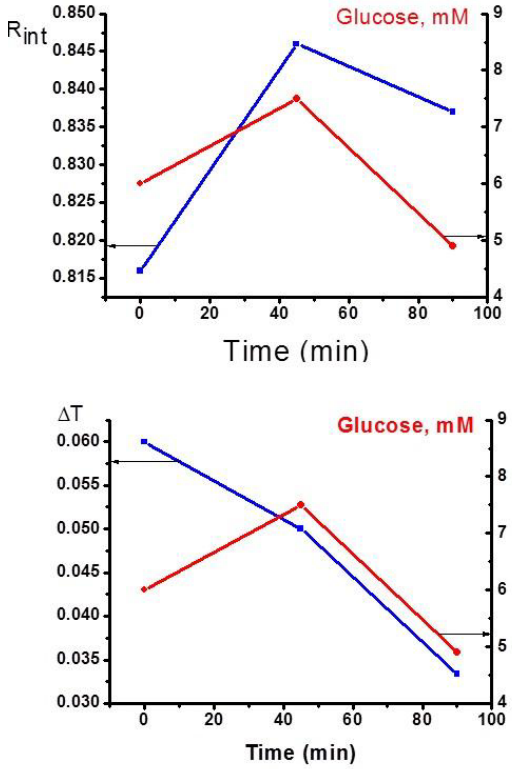

Fig. 2. The ATR amplitude R_{int} and time shift ΔT of human skin and glucose concentration in blood (mM) versus time (min) after glucose intake

The change in the ATR amplitude and phase of skin are determined only by variations of the slow Debye process [7]. When we observe changes of the ATR spectra after ingestion of glucose solution we see the effect that has a high level of blood glucose concentration on tissue and skin.

Conclusion

We showed that diagnostics based on THz time domain spectroscopy allows to make an integral estimation of the content of metabolites in blood plasma and distinguish blood plasma of healthy rats and rats with experimental diabetes of different degrees of severity. To increase diagnostic THz sensitivity we now develop polymer capillary waveguide sensor for such solutions. We expect more sensitivity for refraction changes of the outer media (solution) due to tens of cm interaction length.

The ATR amplitude of human palm skin increased when the glucose concentrations in blood rose above the normal level. The observed change of the spectrum is described with high degree of accuracy by the reduction in the ratio $\Delta\varepsilon_1/\tau_1$ in the Debye model of glucose aqueous solution.

Terahertz Pulsed Spectroscopy can be used as a promising diagnostic method of Diabetes Mellitus.

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