Metformin reacts directly with glucose following the Maillard reaction pathway

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Metformin (dimethylbiguanide) is the preferred first-line oral blood glucose-lowering agent to manage type 2 diabetes. Looking to its activity, Sterne in 1963 suggested for this compound the name 'glucophage' (meaning glucose eater).[1] The generally accepted mechanism of metformin effect is based on the stimulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK). In its turn AMPK is directly activated by an increase in AMP:ATP ratio in metabolic stress conditions, including hypoxia and glucose deprivation. Recently, many novel pathways, besides AMPK induction, have been revealed, which can explain some of other metformin's beneficial effects (reduction in cardiovascular disease and mortality compared with non-intensive treatment and a possible reduction in cancer incidence). The molecular details of metformin mechanism of action continue to be an area of vigorous research. In the review of Pearson et al [2] the known and unknown aspects about the molecular action of metformin have been widely discussed.
In the present study we investigate on an alternative pathway, i.e. on the possible reaction between metformin and circulating glucose, which is present in the range 140-200 mg/dL in diabetic patients. It must be considered that oral doses (from 500 to1000 mg) of metformin are rapidly absorbed in the small intestine, typically giving a peak plasma concentration (Cmax) of about 2 µg/mL (rarely >4 µg/mL), with a steady-state concentration range of 0.3–1.5 µg/mL. Its distribution is extensive (usual volume of distribution [Vd], 100–300 L). Metformin has an elimination half-life (T1/2) of ~6–7 h. [3]
These values suggest that the reaction of metformin (MET) with glucose (GLU) can in principle occur, following the Maillard reaction pathway. This aspect has been studied and the obtained results are reported and discussed in the present investigation. Glucose and metformin reacts with the formation of [GLU+MET – H_2O] (***a***) i.e. the final product of the Maillard reaction. [GLU+MET – $2H_2O$] (***b***) species are also observed in higher abundance. Both ***a*** and ***b*** are detected by HPLC/ESI mass spectrometry operating in high resolution conditions, showing that for both accurate mass measurements are in agreement with the proposed compositions. ***b*** species reasonably originate by the further reactivity of ***a***, due to the presence of other amino groups. Their possible structures have been investigated by MS/MS experiments performed on their protonated species. Interestingly they have been detected in urine samples of subjects under metformin therapy. Consequently not only the action of the unreacted metformin can be considered, but also the products originated by reaction with glucose must be taken in account for their possible activity at systemic level.

[1] Sterne J (1963) Report on 5-years' experience with dimethylbiguanide (metformin, glucophage) in diabetic therapy. Wien Med Wochenschr 113:599–602.

[2] Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? Diabetologia. 2013 Sep;56(9):1898-906.

[3] Scheen AJ (1996) Clinical pharmacokinetics of metformin. Clin Pharm 30:359–371