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Influence of the semisynthetic bile acid (MKC) on the ileal permeation of gliclazide in healthy and diabetic rats

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Abstract:
The aim of this study is to investigate how the semisynthetic bile acid; 3α,7α-dihydroxy-12-keto-5β-cholanate, also known as 12-monoketocholic acid (MKC) influences the ileal permeation of the antidiabetic drug gliclazide in healthy and diabetic rats. Male Wistar rats were divided into 10 groups (n = 32), of which 5 comprised healthy rats (1 to 5) and 5 diabetic rats (6 to 10). Group 1 was used to measure the permeation of gliclazide (200 μg/ml) alone (control) while in groups 2 to 5 gliclazide permeation was measured in the presence of MKC (50 μg/ml), glibenclamide (100 μg/ml), rifampicin (100 μg/ml) and verapamil (30 μg/ml), respectively, using Ussing chambers. Groups 6 to 10 were treated in the same way, after the induction of type 1 diabetes with alloxan (*iv* 30 mg/kg). In tissues from healthy rats, there was a 9-fold reduction in the mucosal to serosal permeation of gliclazide in the presence of MKC ($p < 0.001$) while glibenclamide and rifampicin reduced the permeation of gliclazide in both directions; mucosal to serosal and serosal to mucosal and verapamil had no effect. In contrast, in diabetic rats, there was no net transport of gliclazide alone or after the addition of MKC, glibenclamide, rifampicin or verapamil. The lack of any net flux of gliclazide in diabetic rats suggests the lack of action of drug transporters involved or the suppression of their expression. Furthermore, MKC-induced inhibition of mucosal to serosal unidirectional flux of gliclazide, in healthy rats, can be the result of the selective inhibition of Mrp3.

Key words:
bile acid, gliclazide, glibenclamide, rifampicin, verapamil, permeation, transporters, diabetes