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## Is drug lipophilicity a robust predictor for potency of beta-cell $K_{ATP}$ channel block

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**Introduction** The ability of sulphonylurea drugs to potently inhibit ATP-sensitive-potassium channels ($K_{ATP}$) have revolutionised our understanding and treatment of hypoinsulinaemic disorders such as type II diabetes. However adverse hyperinsulinaemia with a variety of structurally diverse drugs unrelated to of sulphonylureas is demonstrated to arise from off target inhibition of $K_{ATP}$ (1). By a retrospective analysis of published data, I demonstrate that the potency for non-sulphonylurea compounds that inhibit $K_{ATP}$, is dependent on their lipophilicity.

**Methods** Publications that measured $K_{ATP}$ currents with either whole-cell or inside-out patch clamp in pancreatic beta-cells, beta-cell cell-lines or from cells expressing recombinant $Kir6.2_4/SUR1_4$ constructs were examined (1). Log $IC_{50}$ values recorded in the presence of intracellular $Mg^{2+}$, except where $Mg^{2+}$ did not affect drug action, were extracted. Log P values, pH range 7-9, were from DrugBank (2) else they were calculated from quantitative structural activity relationships with Chemicalize (3).

**Results** With the exception of sulphonylureas, the $pIC_{50}$ of 23 drugs to block $K_{ATP}$ were linearly correlated to their Log P ($r = 0.91$, $p < 0.001$). Linear regression revealed a slope coefficient insignificantly different to 1 (0.83 to 1.3, 95% C.I.) and a y intercept of 1.9 (1.3 to 2.6, 95% C.I.); a value indicative of a membrane concentration of 10 mM at the $IC_{50}$ for any drug. Expression studies with $K_{IR}6.2\Delta C26$, which forms $K^+$ channels in the absence of SUR1, show, where tested, that the channel pore is the predominant binding site for non-sulphonylureas (1). This finding is supported by drugs which block $K_{ATP}$ with a potency unaffected by $Mg^{2+}$ a condition which uncouples the interaction between SUR1 and Kir6.2 (1). Further support for these ideas comes from diazoxide which opens $K_{ATP}$in the presence of intracellular $Mg^{2+}$ but blocks in its absence (4) with a $pIC_{50}$ related to its Log P .

**Conclusion** For non-sulphonylurea drugs that inhibit $K_{ATP}$ their $pIC_{50}$ is linearly related to Log P and is devoid of obvious structural or chemical motifs. Moreover, these data suggest that the action of these drugs occurs by a simple physiochemical disruption of the membrane bilayer environment and suggest that a prospective analysis of Log P for new drugs will help predict adverse hypoglycaemic action.

**References** (1) Gribble FM et al (2000) Br. J Pharmacol. 13 (2000) 756-760. (2) Drugbank http://www.drugbank.ca/ (3) Chemicalize www.chemicalize.org/ (4) Kozlowski RZ and Ashford ML (1992) Br. J Pharmacol. 107: 34-43.