Drug Metabolism

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Effect of malathion at subchronic exposure on insulin secretory response of rat isolated pancreatic islets

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Hyperglycemia is one of the side-effects of organophosphate (OP) poisonings and there are some evidences for a relationship between acetylcholinesterase (AChE) inhibition and OP-induced hyperglycemia. Malathion is a widely-used OP with various effects on different organs. To investigate the effects of malathion on insulin secretion by isolated rat islets in pancreas, malathion was administered through food for 4 weeks at concentrations of 100, 200, and 400 ppm; doses were chosen on the basis of effects on AChE activity and NOEL (No Observable Effect Level) (Pournourmohammadi et al 2005). At the end of the specified treatment (18 h fasting after the last dose of malathion), a blood sample was taken under anesthesia by cardiac puncture in vials containing heparin then plasma was separated. The pancreas may then be distended by injecting 10 ml of cold collagenase V (5 mg/ml of HANKS-HEPES) in pancreas and the islets were freshly isolated (Rubi et al 2005). Insulin secretion was assayed in response to basal 2.5 mM, stimulatory 16.7 mM glucose and 2.8 mM glucose plus 30 mM KCl in rat islets, tested over a 30-min stimulation period. Insulin level was assayed using rat insulin ELISA kit. Results indicated that malathion at doses of 200 and 400 ppm increase blood glucose concentrations by 44.4 and 60.6% as well as insulin concentrations by 36.6 and 143.2% of control, respectively. Although in vitro findings showed isolated islets from 4 weeks-pretreated rats with doses of 200 and 400 ppm malathion, in the presence of basal and stimulatory glucose released less insulin secretion (%content) by 57.1% and 69% compared wtih control, respectively, malathion could not change KCl-stimulated insulin secretion. Light microscopic examination revealed that malathion causes patchy degenerative changes developing from 100 ppm to 400 ppm in pancreatic islets. Malathion administration developed hyperglycemia that was not compensated by insulin despite its increased secretion; maybe linked to ACh, which is a potent secretagogue of both insulin and glucagon or detrimental effect of malathion on insulin resistance. The decrease of the glucose-stimulated insulin secretion by isolated islets can be attributed to the ability of malathion to affect the cellular metabolism possibly mitochondrial activity. Furthermore, light microscopic examination in semithin sections revealed that malathion caused patchy degenerative changes with an increasing trend from 100 to 400 ppm in islets, especially in β cells, including some micro and macro vesicles in cytoplasm, hypertrophy, karyorexies, pyknosis, necrosis and congestion, suggesting that malathion can influence insulin secretory function of pancreatic islets in vivo and in vitro.

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Captopril prodrugs for transdermal delivery: docking and metabolism with CYP4502c1, RNase, and acetylcholinesterase

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A series of straight chain and branched chain ester prodrugs of captopril have been developed as potential candidates for transdermal delivery. In vitro percutaneous absorption experiments have determined that the flux of the prodrugs are substantially enhanced compared to the parent drug (Moss et al 2006). For bioavailability issues it is also necessary to investigate the metabolism of the prodrugs by the in vitro and ex vivo evaluation of the ester hydrolysis rate. However, in this parallel study we are interested in investigating the influence of molecular structural change on ester metabolism rate in silico. A series of experiments were performed computationally using molecular modelling and automated molecular docking techniques. The captopril ester prodrugs (ligands) were modelled and then automatically docked with three different protein receptors using Autodock (version 3.0.5). The first series of experiments involved holding captopril static, while the second series of experiments allowed free rotation about carefully chosen bonds in the molecule. The Autodock program predicts the energy interaction of ligands with biomacromolecular targets by calculating energy minima by a simulated annealing technique as the ligand performs a random "walk" around the static protein (Morris et al 1998). For each prodrug, the docking algorithm was repeated 100 times for static ligands, and 250 times for flexible ligands. AutoDock then presented minimum energy cluster histograms from which it is possible to isolate coordinates of lowest energy docking sites. These docking sites represent the areas on the proteins that are most likely to be involved in ester hydrolysis. According to the Michaelis-Menten equation, a high affinity produces a low rate of reaction between an enzyme and a substrate (Lehringer 2005). Therefore, the ligands with the highest energy (lowest affinity) should display the fastest rate of metabolism. The findings from these studies support the findings from the previously performed in vitro metabolism experiments, with an r^2 value of 0.91 when in vitro metabolism experiments are compared with modelling studies (Moss et al 2006). This study highlights molecular modelling as a potential tool for predicting trends in protein/substrate interactions, even though no direct relationship between calculated energy minima and experimentally determined rates has been established.

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