ABSTRACT

A Comparative Study of the Diabetogenic Effects of Streptozotocin and Alloxan Monohydrate in Rats.

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In this thesis, **Streptozotocin (STZ)** and **alloxan (AX) models** of experimental diabetes mellitus were compared in rats. In acute studies, both agents produced hyperglycaemia within 2 hours of injection, followed by hypoglycaemia which was reconverted to hyperglycaemia between 8 and 24 hours after injection of the agents. These glycaemic responses corresponded with changes in plasma insulin concentration reflective of alterations in pancreatic β-cell responsiveness. There was also evidence of pancreatic cellular damage as early as 4 - 7 hours after injection of the agents. However, after pre-treatment with indomethacin, diabetes was not induced by streptozotocin, but it was induced by alloxan after a delay of 14 days. By contrast, the reducing agents glutathione and cysteine only delayed the onset of streptozotocin-induced diabetes, but alloxan-induced diabetes was unaffected. Subsequent to these initial events, there was establishment of diabetes mellitus at least 10 days after injection of each agent. But, the severity of the diabetes as well as the induction potential of the drugs depended on the dose and the age of the rats. For example streptozotocin (60 mg/kg) did not induce diabetes

in rats 3 days old, whereas alloxan (70 mg/kg) was lethal to rats of this age. However, streptozotocin (60 mg/kg) did induce diabetes mellitus in rats 38 days old, but alloxan (70 mg/kg) did not induce diabetes mellitus in these rats. Alloxan (70 mg/kg) did however, induce diabetes mellitus in 59 days old rats.

In the long-term study (up to 1 year), most rats from both diabetic models showed pathological features such as cataracts, decreased muscle mass, skin changes, polyphagia, polyuria, polydipsia and persistent hyperglycaemia. Additionally, there was evidence of reversibility of the diabetic state in terms of the tendency for normalization of the blood glucose concentration in both diabetic models; but these rats still showed evidence of pancreatic damage and reduced responsiveness to an oral glucose load.

These findings suggest that both agents produced their diabetogenic effects quite rapidly, but whereas an inflammatory reaction may be involved in the initiating phase of streptozotocin induced diabetes mellitus, a more complex reaction, possibly involving DNA damage may be responsible for the alloxan induced diabetes mellitus. Also, the findings suggest that compared to alloxan, the streptozotocin model of diabetes provides greater flexibility for experimental use in terms of the ability to produce variable degrees of diabetes mellitus with minimum toxicity.