Sriram, K., and O'Callaghan, J.P.: Obesity as a potential risk factor for susceptibility to neurotoxic insult. The Toxicologist 54: 22, 2000

Obesity is a major risk factor associated with a variety of diseases including cardiovascular disorders, diabetes and certain cancers. Little information exists, however, as to whether obesity modifies the response of the central nervous system (CNS) to neural injury. The purpose of the present study was to determine if obesity serves as a predisposing factor in modifying/mediating a neurotoxic response. Leptin deficient (*ob/ob*) mice were used as a model of obesity and the dopaminergic neurotoxicants, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and methamphetamine (METH) were used as neurotoxic insults. Tyrosine hydroxlase (TH) was used as an index of dopaminergic nerve terminal integrity and was assessed by a novel fluorescence-based ELISA and by immunoblot. Glial fibrillary acidic protein (GFAP) was used as an index of the glial reaction to terminal damage and was assessed by sandwich ELISA. Both MPTP and METH significantly decreased striatal TH levels in a time-dependent fashion in the striatum of wild and *ob/ob* mice. Basal levels of TH were 25% lower in ob/ob mice compared to wild type mice. By 48 hours post-dosing, MPTP reduced TH by approximately 70-75% in both wild type and *ob/ob* mice. METH resulted in nearly a 90 % decrease in ob/ob mice in comparison to 75% decrements in wild type controls. These data were in agreement with immunoblot results on the same samples. While both MPTP and METH induced a large (>600%) increase in striatal GFAP of wild-type mice, this effect was attenuated (not exacerbated) in *ob/ob* mice. Basal levels of GFAP also were lower (25%) in *ob/ob* mice. The data indicate that METH-induced dopaminergic neurotoxicity (based on TH decreases) is enhanced in the obese (*ob/ob*) and that the leptin-deficient condition decreases the levels of TH and GFAP. The *ob/ob* mouse may not serve as an appropriate model for assessing the effects of obesity on toxic responses of the CNS.