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METH intoxication report no decrement in postmortem measures of [3H]-dihydrotrabenazene (DTBZ) binding to the neuronal vesicular monoamine transporter (VMAT2). This finding in humans, which is unexplored in mice, is unexpected in light of significant decrements observed in other neurochemical indices. In the present studies, [3H]-DTBZ binding was performed in striatal homogenates of METH-treated mice at time points between 1-85 days post-METH. These studies reveal that VMAT2 binding in striatal homogenate may not be a reliable index of nerve terminal loss at early time points (1-4 days) following METH intoxication. In contrast to significant loss of other neurochemical indices, [3H]-DTBZ homogenate binding gradually declined. On day 1 [3H]-DTBZ homogenate binding was not significantly decreased (-8%); by day 2, however, binding showed a significant decline (-34%), reaching a nadir by day 4 (-60%). To explore differences between [3H]-DTBZ binding and other measures of nerve terminal loss, [3H]-DTBZ homogenate binding was compared to [3H]-DA uptake into striatal vesicles 1 day post-METH. This measure of vesicular function was readily compromised, which is consistent with the early compromise of DAT(-77%) and TH (-65%). These results suggest that [3H]-DTBZ binding in homogenate may not adequately reflect nerve terminal status at early time points. However, at time points after day 4, loss of [3H]-DTBZ binding in homogenate (-60%) closely paralleled loss of TH activity (-51%). Over the course of 85 days, loss of [3H]-DTBZ binding and TH activity were not as substantial as loss of DAT binding and DA content. Recovery of measures occurred at the same rate; although measures demonstrating recovery persisted below control values, indicating a lasting neurotoxic effect in METH-treated mice.

61 THE TRIGGERING ROLE OF DOPAMINE IN NEUROTOXIC DAMAGE CAUSED BY AMPHETAMINE.

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The breakdown products of dopamine (DA) are potentially neurotoxic but neuronal damage due to amphetamine (Amph) treatment may not only be produced by DA radical metabolites. The aim of present study was to explore the relationships between extracellular DA, glutamate (Glu) and taurine (Tau) and hydroxyl radical (OH \cdot) generation during subchronic Amph treatment (5 mg/kg, 4 injections i.p. with 2-hour intervals). The extracellular levels of DA, Glu and Tau were estimated by means of HPLC and the generation of OH \cdot with salicylate method in the rat neostriatum by microdialysis. Amph caused an immediate increase in the extracellular DA concentration up to 950%, which effect was quickly reduced to the baseline values. The subsequent Amph injections were followed by a much smaller increase in the extracellular DA concentration (about 300%). Amph produced marked increase in the OH \cdot generation, the first wave was observed 80 min after the second injection and persisted during 2 hours (up to 700%), and the second increase occurred after the 4-th injection (up to 400%). Amph (5 mg/kg) caused a marked gradual increase in the Glu and Tau levels (up to 500 and 450% of the pre-drug value, respectively) by the end of experiment. Our results suggest a triggering role DA in neurochemical changes which lead to neuronal damage. The changes in extracellular DA, Glu, Tau and OH \cdot reflect different subsequent phases of Amph neurotoxicity.

62 IDENTIFICATION OF A PROTECTIVE RESPONSE IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE.

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Alzheimer's disease (AD) is associated with increased levels of the toxic peptide, β -amyloid (A β). This disease is modeled in Tg2576 mice by overexpression of a mutant form of human amyloid precursor protein (HuAPP_{sw}). However, despite high A β levels, plaques do not develop in these mice until an average age of 12 months, and there is no neuronal loss in the hippocampus of mice as old as 16 months. Using an Affymetrix microarray system, we compared mRNA expression levels in the hippocampus and cerebellum of three six-month-old HuAPP_{sw} mice to three age-matched, non-transgenic controls. A ranking analysis based on Affymetrix's difference call was used to determine significant increases and decreases. RT-PCR of selected genes confirmed our results. Microarray analysis of the hippocampus demonstrated increased expression of transthyretin (TTR; 29.5-fold), a protein shown to sequester A β and prevent plaque formation, as well as a number of genes involved in neuronal proliferation, differentiation, and tissue remodeling. Of the 23 genes increased in the hippocampus, five were involved in growth factor pathways. Three genes involved in the activation of the insulin-signaling pathway were differentially regulated, including a 16.6-fold increase in insulin-like growth factor 2 (IGF2). Immunohistochemistry confirmed the hippocampal increases of TTR and IGF2. The cerebellum is typically unaffected in AD and does not develop a significant age-dependent increase in A β levels in HuAPP_{sw} mice. When comparing the cerebellar gene expression in HuAPP_{sw} mice to controls, the fold increase of TTR was reduced to 3.2-fold. Other genes differentially regulated in the hip-

pocampus showed no changes at all in the cerebellum. Therefore, the slow progression and lack of full-fledged pathology in the hippocampus of HuAPP_{sw} mice may result from the increased expression of protective and growth-inducing genes. Specifically, TTR and the insulin-signaling pathway may play an important role in mediating this protective response. (Support: ES08089, ES10042, & BWF New Investigator Award).

63 OXIDATIVE DNA DAMAGE PRECEDES AMYLOID PLAQUE FORMATION IN AMYLOID PRECURSOR PROTEIN (APP) TRANSGENIC MICE: AN ANIMAL MODEL OF ALZHEIMER'S DISEASE.

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Reactive oxygen species (ROS) are implicated in neurodegenerative conditions such as Alzheimer's disease (AD), but their role in the mechanism of neurotoxicity is unclear. Here, we provide the first evidence that DNA oxidation precedes amyloid plaque formation in amyloid precursor protein (APP) mice, a transgenic mouse model of AD. To determine the relation of oxidative DNA damage, lipid peroxidation and amyloid beta (A β) plaque deposition, a characteristic hallmark of AD, we examined the frontal cortex, hippocampus and cerebellum of APP mice, compared to age-matched wild-type controls, for endogenous DNA oxidation evidenced by 8-oxo-2'-deoxyguanosine formation, and lipid peroxidation determined by thiobarbituric acid reactive substance formation. In the frontal cortex, oxidative DNA damage was enhanced within 6 weeks in APP mice, peaked at 5 months (p<0.01) and returned to basal levels by 7 months. DNA oxidation was similarly elevated in hippocampal but not cerebellar tissues. In contrast, plaque formation was not observed until after 3 months of age in the frontal cortex and hippocampus, nor was lipid peroxidation elevated in any tissue at any age. These results suggest that ROS-mediated oxidation of oligonucleotides, as distinct from lipid, may constitute an early event in the pathogenesis of AD. (Support: Canadian Institutes of Health Research)

64 POTENTIAL ROLE OF MITOCHONDRIAL COMPLEX II ACTIVITY IN REGIONAL DIFFERENTIAL CNS SENSITIVITY TO 1, 3-DINITROBENZENE-INDUCED ENCEPHALOPATHY.

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Exposure to 1, 3-dinitrobenzene (DNB) produces an edematous, glio-vascular lesion that is initially confined to brainstem nuclei with high energy requirements. Selective vulnerability of brainstem astrocytes to DNB is mediated by a ten-fold lower threshold for opening of the mitochondrial permeability transition (MPT) pore. Exposure of brainstem astrocytes to 100 μ M DNB results in complete loss of mitochondrial membrane potential by 10 min, while their cortical counterparts remain unaffected for at least 1 hour. However, the loss of membrane potential in brainstem astrocytes is prevented by pretreatment with the known MPT pore inhibitor, cyclosporin A (CsA). DNB also decreases mitochondrial reducing potential by inhibiting FAD-linked reduction at complex II. Therefore, it is hypothesized that inhibition of mitochondrial complex II (succinate dehydrogenase) is causally linked to regional differences in susceptibility to activation of the MPT by DNB. Using cultured neonatal rat brainstem and cortical astrocytes, complex II was localized histochemically. Complex II activity is significantly inhibited in both brainstem and cortical astrocytes at 0.5, 2, 5, and 24 hours following *in vitro* exposure to 100 μ M DNB. Although the observed inhibition of SDH was prevented by pretreatment CsA in brainstem astrocytes after 0.5 and 2 hours, CsA pretreatment failed to significantly prevent inhibition of complex II activity in cortical astrocytes. These results suggest that either 1) inhibition of complex II is independent of the mechanism of DNB-induced opening of the MPT, or 2) differential regional regulation of the MPT subsequent to inhibition of complex II confers anatomical protection/vulnerability. However, the possibility that complex II activity is directly inhibited by DNB remains to be determined.

66 ANTIOXIDANT PROTECTION AGAINST ETHANOL-INDUCED CELL LOSS IN CEREBELLAR GRANULE CELL CULTURES.

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Ethanol exposure during development can cause decreases in neuronal cell populations resulting in permanent neurological deficiencies. Cerebellar granule cell cultures are vulnerable to ethanol toxicity and are useful for investigating mechanisms