in PD. Decreased Cu was also seen in ILBD, a disorder suggested to represent preclinical PD, suggesting this change occurs early in these synucleinopathies. Our findings may be relevant for Cu-containing proteins, such as superoxide dismutase and alpha-synuclein, thought to be involved in degenerative mechanisms in parkinsonian syndromes.

P3.053
Up-regulation of divalent metal transporter 1 in 6-hydroxydopamine intoxication is IRE/IRP dependent

H. Jiang, N. Song, L. Hou, H. Xu, S. Zhang, J. Xie. *State Key Disciplines: Physiology (in incubation); Department of Physiology, Qingdao University, Qingdao, China*

Iron plays a key role in Parkinson's disease (PD) and increased iron content was found in the substantia nigra (SN) in PD patients. Divalent metal transporter 1 (DMT1) was up-regulated in the SN of both MPTP-induced PD models and PD patients. However, what are the mechanisms underlying DMT1 up-regulation is largely unknown. In the present study, we first observed DMT1 with the iron responsive element (IRE, DMT1+IRE) but not DMT1 without IRE (DMT1−IRE) was up-regulated *in vivo* in the SN of 6-hydroxydopamine (6-OHDA)-induced PD rats, suggesting increased DMT1+IRE expression might account for the nigral iron accumulation in PD rats. This was futher confirmed by our *in vitro* study in 6-OHDA-treated and DMT1+IRE over-expressed MES23.5 cells, respectively. Increased iron regulatory protein (IRP) 1 and IRP2 expression were observed, while silencing of IRPs dramatically diminished 6-OHDA-induced DMT1+IRE up-regulation. Pretreatment with N-acetyl-L-cysteine could fully suppress IRPs up-regulations by inhibiting 6-OHDA-induced oxidative stress. Our data gave the direct evidence that DMT1+IRE up-regulation accounted for 6-OHDA-induced iron accumulation in an IRE/IRP-dependent manner, which was initiated by 6-OHDA-induced intracellular oxidative stress. Increased intracellular iron thus resulted in aggravated oxidative stress. This study might support the use of anti-oxidants in the treatment of PD from a quite new angel, which could inhibit iron accumulation by regulating DMT1 expression.

P3.054
Effect of prenatal manganese intoxication on dopaminergic neurotranssmision in the brain of rats lesioned as neonates with 6-hydroxydopamine

P. Nowak[1], A. Kwiecinski[1], R.M. Kostrzewa[2]. [1]*Pharmacology, University, Zabrze, Poland;* [2]*Pharmacology, University, Johnson City, TN, USA*

The effects of prenatal manganese (Mn) intoxication on reactivity of central dopamine receptors and dopamine (DA) metabolism were studied in rats lesioned as neonates with 6-hydroxydopamine (6-OHDA). $MnCl_2 \times 4H_2O$ (10,000 ppm) was added to the drinking water of Wistar pregnant rats for the duration of pregnancy. On the day of parturition Mn was discontinued as an additive in the drinking water. The control group consisted of rats that consumed water without Mn. At 3 days after birth rats of both examined groups (control and Mn) were pretreated with desipramine HCl (20 mg/kg) and pargyline HCl (50 mg/kg) and injected bilaterally *icv* with 6-OHDA HBr in one of three doses (15 μg, 30 μg or 67 μg base form on each side, or the vehicle saline) (control). At 8 weeks after birth rats were injected with either SKF 38393 (DA D1 agonist), apomorphine (DA D2 agonist), quinpirole (DA D2/D3 agonist), SCH 23390 (DA D1 antagonist) or haloperidol (DA D2 antagonist), and were tested for characteristic behavioral effects: oral movements, yawning, stereotypy and catalepsy. Furthermore DA and its metabolites as well as DA-synthesis rate in the frontal cortex, hippocampus, striatum, hypothalamus, cerebellum and brain stem were evaluated. It was shown that Mn intoxication produced disturbances mainly in corticolimbic DA neurotransmission. Moreover based on behavioral data we demonstrated that Mn increased the vulnerability to neurotoxic effects of the 15 μg dose of 6-OHDA.

P3.055
Welding fume-related dopaminergic neurotoxicity

K. Sriram, G.X. Lin, A.M. Jefferson, O. Wirth, Y. Hayashi, J.R. Roberts, R.S. Chapman, K.M. Krajnak, J.M. Antonini. *CDC-NIOSH, Morgantown, WV, USA*

Manganese (Mn) intoxication is associated with increased prevalence of neurological conditions resembling Parkinson's disease (PD). The presence of Mn in welding consumables therefore raises concerns about potential neurological risks following occupational exposure to welding fume (WF). To investigate if WF exposure induces neurotoxicity, we treated rats with low- and high-Mn containing WF. Repeated intratracheal instillations (0.5 mg/rat, 1/wk × 7 wks) of gas metal arc-mild steel (GMA-MS; low Mn, insoluble) or manual metal arc-hard surfacing (MMA-HS; high Mn, soluble) fumes caused loss of tyrosine hydroxylase (TH) protein in the striatum (~20%) and midbrain (~30%) by 1 d post-exposure. While loss of TH following GMA-MS was transient, a sustained loss was observed in the midbrain (34%) even after cessation of MMA-HS exposure. Both fumes caused down-regulation of D2 receptor (30–40%) and Vmat2 (30–55%) mRNAs in the midbrain. A different exposure paradigm (2 mg/rat, 1/wk × 28 wks) resulted in loss of Park 5 and Park 7 proteins in striatum (40–50%), but not midbrain. A similar regimen of $MnCl_2$ caused extensive loss of these proteins in both striatum (70–80%) and midbrain (60%). All treated animals exhibited hyperactivity but not deficits in gross-motor behavior. As mutations in PARK genes have been linked to onset of PD and because welding is implicated as a risk factor for idiopathic PD, it remains to be elucidated if PARK genes have an underlying role in the pathogenesis of WF-induced neurodegeneration. Our findings suggest that Mn-containing WF can cause persistent alteration of several PD-related genes that could lead to dopaminergic neurodegeneration.

P3.056
The relationship between blood levels of heavy metals and Parkinson's disease in China

X. Tan. *School of Public Health, Wuhan University, Wuhan, China*

Background: It is well known that idiopathic Parkinson's disease (PD) and the Parkinsonian syndrome caused by manganese (Mn) poisoning are undistinguishable in the symptoms. So we doubt there are many patients who have accumulated Mn in the body in daily life and are diagnosed as idiopathic PD. We examined the relationship between PD and blood levels of heavy metals, and the influence of their intake from food in a population in general environment.
Methods: The subjects comprising PD patients and sex- and age-matched controls were recruited from the outpatient clinic of Xiangfan No. 1 People's Hospital in Hubei, China between 2006 and 2008. Previous eating habits etc. before they were diagnosed with PD were asked. The morning blood samples were collected before breakfast and were used to measure concentrations of metals.
Results: Whole blood Mn and serum iron (Fe) levels were significantly higher in PD patients than in controls. But no differences were seen in intake of each metal from food, experience of Mn poisoning between groups.
Conclusions: In China, accumulation of Mn and Fe from unknown route might be involved in the etiology of PD in a general population.