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Reactive gliosis, characterized by the accumulation of glial fibrillary acidic protein (GFAP), is the earliest and most common cellular response diverse neural insults. The present study sought to delineate, in vivo, the involvement of MAPK- and JAK-STAT-related signaling programs involved in neurotoxicant-induced GFAP up regulation. The dopaminergic neurotoxicants, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP, 12.5 mg/kg, s.c.) and methamphetamine- (METH, 8 mg/kg, s.c.) were used to injure the striatum. Control and treated, female, C57BL/6J mice were sacrificed at specific following exposure intervals (hours, days & weeks), by decapitation or focused microwave irradiation, a technique that rapidly inactivates metabolic activity, preserving steady state protein modification. Striatal (target) and non-target (hippocampus) homogenates were assayed for injury-induced changes in markers of dopamine neuronal integrity as well as differences in the levels of activated phosphoproteins. Two days following exposure GFAP induction reached a maximum, and was declining to baseline levels at 2 wks. Neurotoxicant-induced reductions in striatal levels of DA and tyrosine hydroxylase (TH) paralleled the temporal profile of GFAP induction. Blots of striatal homogenates probed with phosphorylation-state specific antibodies, demonstrated significant changes in activated forms ERK 1/2, JNK, MEK1/2, p70 S6 kinase, CREB, and Stat3 as early as one hour after insult, with the largest activation at time points (6 and 12h) preceding the peak induction of GFAP (48h post treatment). Nomifensine pretreatment pretreatment (25 mg/kg, s.c. 30 min prior to MPTP administration) antagonized both the cellular and molecular changes associated with glial induction. Curiously, striatal homogenates obtained from decapitated mice, exhibited aberrant phospho-reactivity, suggesting provisional inhibition of phosphophatase activity, that was neither time nor cascade dependent. Common MAPK and JAK-STAT neurotoxicant-induced signaling suggest cellular events upstream of gliosis, which may serve as potential targets for modulation of the neural injury response.