Methamphetamine neuroprotection

Traumatic brain injury

In a 2008 study, O'Phelan et al. reported that severe traumatic brain injury (TBI) patients that tested positive for methamphetamine at the time of admission, had a significant, though unexplained, decrease in mortality (odds ratio of 0.25 (p = 0.02)) [1].

Ding et al assessed the effects of low dose methamphetamine treatment of traumatic brain injury (TBI) in rats by employing MRI, immunohistology, and neurological functional tests. Young male Wistar rats were subjected to TBI using the controlled cortical impact model. The treated rats (n=10) received an intravenous (iv) bolus dose of 0.42 mg/kg of methamphetamine at eight hours after the TBI followed by continuous iv infusion for 24 hrs. The control rats (n=10) received the same volume of saline using the same protocol. MRI scans, including T2 weighted imaging (T2WI) and diffusion tensor imaging (DTI), were performed one day prior to TBI, and at 1 and 3 days post TBI, and then weekly for 6 weeks. The lesion volumes of TBI damaged cerebral tissue were demarcated by elevated values in T2 maps and were histologically identified by hematoxylin and eosin (H&E) staining. The fractional anisotropy (FA) values within regions-of-interest (ROI) were measured in FA maps deduced from DTI, and were directly compared with Bielschowsky's silver and Luxol fast blue (BLFB) immunohistological staining. No therapeutic effect on lesion volumes was detected during 6 weeks after TBI. However, treatment significantly increased FA values in the recovery ROI compared with the control group at 5 and 6 weeks after TBI. Myelinated axons histologically measured using BLFB were significantly increased ($p<0.001$) in the treated group (25.84±1.41%) compared with the control group (17.05±2.95%). Significant correlations were detected between FA and BLFB measures in the recovery ROI ($R=0.54$, $p<0.02$). Methamphetamine treatment significantly reduced modified neurological severity scores from 2 to 6 weeks ($p<0.05$) and foot-fault errors from 3 days to 6 weeks ($p<0.05$) after TBI. Thus, the FA data suggest that methamphetamine treatment improves white matter reorganization from 5 to 6 weeks after TBI in rats compared with saline treatment, which may contribute to the observed functional recovery [2].

A small study demonstrates that tissue metabolism is regionally heterogeneous after TBI and pericontusional perfusion was significantly reduced in the Methamphetamine subgroup [3].

Rau et al. published data that showed low dose of methamphetamine is neuroprotective when delivered 3 h after a severe traumatic brain injury (TBI). In a study, they further characterized the neuroprotective potential of methamphetamine by determining the lowest effective dose, maximum therapeutic window, pharmacokinetic profile and gene expression changes associated with treatment. Graded doses of methamphetamine were administered to rats beginning 8 h after severe TBI.

They assessed neuroprotection based on neurological severity scores, foot fault assessments, cognitive performance in the Morris water maze, and histopathology. We defined 0.250 mg/kg/h as the lowest effective dose and treatment at 12 h as the therapeutic window following severe TBI.

They examined gene expression changes following TBI and methamphetamine treatment to further define the potential molecular mechanisms of neuroprotection and determined that methamphetamine significantly reduced the expression of key pro-inflammatory signals. Pharmacokinetic analysis revealed that a 24-hour intravenous infusion of methamphetamine at a dose of 0.500 mg/kg/h produced a plasma Cmax value of 25.9 ng/ml and a total exposure of 544 ng/ml over a 32 hour time frame. This represents almost half the 24-hour total exposure predicted for a daily oral dose of 25mg in a 70 kg adult human. Thus, it is demonstrated that methamphetamine is

neuroprotective when delivered up to 12 h after injury at doses that are compatible with current FDA approved levels [4] [5].

3,4-Methylenedioxymethamphetamine (MDMA, or “Ecstasy” in tablet form) is a powerful sympathomimetic drug that is commonly perceived as safer than other stimulants such as methamphetamine or cocaine. “Molly” is a purified form of MDMA that is perceived by users as being even safer, as it is free of adulterants such as methamphetamine. Previously, all reports of intracranial hemorrhages in MDMA abusers were associated with coingestion of other sympathomimetic drugs, or with pre-existing cerebrovascular lesions. We describe a series of three young, otherwise healthy patients with various types of intracranial hemorrhages associated with “Molly” ingestion. All three patients underwent extensive workup including catheter angiography that did not demonstrate aneurysm, arteriovenous malformation, or vasculitis. We suggest that even the purified form of MDMA can cause serious intracranial hemorrhagic complications and should not be thought of as a safe recreational drug [6].

1)
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