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Methamphetamine- and Trauma-Induced Brain Injuries: Comparative Cellular and Molecular Neurobiological Substrates

Mark S. Gold[1,2,3,Ψ], **Firas H. Kobeissy**[1,2,Ψ,†], **Kevin K.W. Wang**[1,5,Ψ], **Lisa J. Merlo**[2], **Adriaan W. Bruijnzeel**[2], **Irina N. Krasnova**[4], and **Jean Lud Cadet**[4]

[1]Center for Neuroproteomics and Biomarkers Research, McKnight Brain Institute of the University of Florida, Gainesville, FL 32610, USA

[2]Department of Psychiatry, College of Medicine, McKnight Brain Institute of the University of Florida, Gainesville, FL 32610, USA

[3]Department of Community Health and Family Medicine, McKnight Brain Institute of the University of Florida, Gainesville, FL 32610, USA

[4]Molecular Neuropsychiatry Branch, National Institute on Drug Abuse, Intramural Research Program, NIH/DHHS, Baltimore, MD 21224, USA

[5]Banyan Biomarkers Inc., 12085 Research Drive, Alachua, FL 32615, USA

Abstract

The use of methamphetamine (METH) is a growing public health problem because its abuse is associated with long-term biochemical and structural effects on the human brain. Neurodegeneration is often observed in humans as a result of mechanical injuries (e.g. traumatic brain injury, TBI) and ischemic damage (strokes). In this review, we discuss recent findings documenting the fact that the psychostimulant drug, METH, can cause neuronal damage in several brain regions. The accumulated evidence from our laboratories and those of other investigators indicates that acute administration of METH leads to activation of calpain and caspase proteolytic systems. These systems are also involved in causing neuronal damage secondary to traumatic and ischemic brain injuries. Protease activation is accompanied by proteolysis of endogenous neuronal structural proteins (αII-spectrin and MAP-tau protein) evidenced by the appearance of their breakdown products after these injuries. When taken together, these observations suggest that METH exposure, like TBI, can cause substantial damage to the brain by causing both apoptotic and necrotic cell death in the brains of METH addicts who use large doses of the drug during their lifetimes. Finally, because METH abuse is accompanied by functional and structural changes in the brain similar to those in TBI, METH addicts might experience greater benefit if their treatment involved greater emphasis on rehabilitation in conjunction with the use of potential neuroprotective pharmacological agents such as calpain and caspase inhibitors similar to those used in TBI.

†Manuscript Correspondence to: Dr. Firas Kobeissy, firasko.ufl.edu; fax 352-392-2579 McKnight Brain Institute Department of Psychiatry University of Florida, PO Box 10015 Gainesville, FL 32610 100 S. Newell Dr. Phone Office : 352-294 0407.
Ψauthors contributed equally

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Introduction

Substance use disorders are chronic relapsing conditions that are very prevalent throughout the world. These drugs are thought to impact or "highjack" the brain's motivational and reward centers, which then mediate the long-term usage of these drugs (1). Furthermore, the discontinuation of drug self-administration leads to negative emotional states that may provide additional motivation for the continuation of drug abuse (2). Although these ideas have influenced basic and clinical research related to the rewarding effects of drugs of abuse and drug withdrawal, they have not led to substantial revolution in our treatment of the cognitive deficits in drug abusing individuals. In fact, many fundamental issues regarding the long-term effects of drugs of abuse remain to be elucidated. For example, it has not yet been determined if there exist specific markers of addiction and recovery. It is still not clear if drug addiction is associated with permanent drug-mediated biochemical and structural changes in the human brain. Given the presence of neuropsychiatric disorders in many drug abusers, it will be important to decipher the neuropathological substrates for the signs and symptoms that impact patients' daily activities. The accumulated evidence suggests that some drugs can cause inflammatory responses, substantial loss of neurotransmitters, as well as neuronal death in animal models using these drugs to mimic the human conditions (3). Thus, the purpose of this review is to compare and contrast the cellular and molecular events that occur in two brain disorders, namely traumatic brain injury (TBI) and methamphetamine (METH) abuse. These data will then be used as a springboard to suggest that METH addicts might benefit substantially from long-term rehabilitative approaches in conjunction with neuroprotective agents similar to those used in trauma patients.

Traumatic Brain Injury

Neuropsychiatric complications of TBI

TBI occurs when the brain is damaged after being impacted by an external force to the head region (4). There are more than two million TBI incidents per year (5). These injuries result in 500,000 hospitalizations, 80,000 patients with long term disabilities, and 100,000 deaths annually in the US. The symptoms of TBI can vary from mild to severe. The patients can complain of headache, confusion, blurred vision, behavioral changes, mood disorders, and other neurological symptoms (6,7). Longterm deficits correlate with pathological changes on CAT scans or MRI (8,9). Neuroimaging studies have revealed significant reduction in hippocampal volume and enlargement of the lateral ventricles (8). Detailed neuropsychological assessments have revealed deficits in attention and processing (10). Successful rehabilitation strategies that address cognitive and other functional deficits in these patients include intensive neuropsychological interventions and the use of pharmacological agents to enhance cognitive improvements (11).

Mechanisms of TBI-induced cell death

Studies assessing the bases of TBI-induced neuropathological changes have depended mostly on animal models (12). These investigations have lead to the conclusion that the pathological substrates of TBI are secondary to a two-step mechanism which involved primary and secondary injuries (13). The primary injury results in the compression of neuronal, glial, astrocytic and vascular tissue (13). The primary injury is associated with disruption of cell

membrane and disturbances of ionic homeostasis as a consequence of membrane leakiness (13,14). The initial impact to the brain has been shown to activate multiple death pathways which include activation of calpains (calcium-dependent protease with papain) and caspases protease systems (4,14).

Secondary injuries proceed within minutes to days after head injury and culminate in widespread cell death (4,15). TBI-induced cell death is accompanied by release of excitatory amino acids, increased production of reactive oxygen species (ROS), and disruption of mitochondrial bioenergetics, disturbances in calcium homeostasis, and neuroinflammatory responses such as reactive gliosis (14,16,17). These disturbances are then accompanied by the activation of a cascade of events which include activation of calcium-dependent enzymes, destruction of the cellular architectures, and ultimately the demise of various cell types in the brain (17,18). This cellular demise occurs via the activation of both necrotic and apoptotic death pathways (16).

Necrosis and apoptosis are two different forms of cell death with different implications for the surrounding tissues (19). Necrosis is a very rapid form of death that can affect large cell populations (20). It results from environmental perturbations (physical and chemical insults) leading to cellular injury. These injuries result in a massive increase in calcium influx that causes cell swelling and nonspecific DNA damage. This is coupled with spillage of intracellular content to the extra-cytoplasmic space, which leads to surrounding tissue inflammation concomitant with calpain protease activation. Apoptotic cell death, also referred to as programmed cell death or type I cell death, is characterized by cell shrinkage, changes in nuclear morphology, blebbing of the plasma membrane, and formation of apoptotic bodies (20). Biochemically, apoptosis is characterized by the activation of cysteine proteases called caspases. Upon activation, caspases act on a number of cytosolic, cytoskeletal and neuronal protein substrates including DNA function related factor-45 (DFF-45), lamin A, poly (ADP-ribose) polymerase (PARP) and αII-spectrin (21). Apoptosis can occur via activation of intrinsic and extrinsic pathways. The intrinsic pathway involves release of several proteins from the mitochondria and subsequent activation of caspase 9 and caspase 3, and caspase-3-mediated destruction of cytoplasmic and nuclear proteins (22-24). The extrinsic pathway is initiated via ligation of death receptors (FasL/Fas pathway) which results in the aggregation of the adaptor molecule Fas-associated death domain (FADD) and activation of caspase-8 (25,26). Activation of caspase-8 leads activation of caspase-3 and to the truncation of the pro-apoptotic Bcl-2 family protein, Bid, which activates the release of pro-apoptotic proteins form the mitochondria (26,27).

TBI-induced cell death has been shown to involve activation of the calpain family of proteases. Calpains are cytoplasmic, calcium-activated neutral cysteine proteases (19). Calpains reside in the cytosol as pro-calpain and translocate to the plasma membrane in response to increased Ca^{2+} levels (19). Calcium induces structural changes leading to calpain activation via the autolytic processing of calpain molecules, generating a smaller functional unit. Among the 14 identified mammalian calpains, two calpains are known to be active after TBI including μ-calpain or calpain-1 which requires micromolar of Ca^{2+} for activation and m-calpain or calpain-2 which requires millimolar of Ca^{2+} for activation (19,28). Upon their activation, calpains cause the degradation of and the appearance of unique breakdown products of various proteins which include cytosolic collapsin response mediator protein-2 (CRMP-2), cytoskeletal αII-spectrin, neurofilament protein, PARP protein and microtubule associated protein-2 (MAP-tau) (29-38). Although calpain activation has been associated mainly with necrotic cell death, some recent studies have also demonstrated their potential involvement in some models of apoptosis (39,40). Nevertheless, TBI-induced apoptosis appears to involve mainly the activation of caspase-3 (41,42).

Neuronal Cell Death and Degradomics Patterns in TBI

Among the proteins, which have been extensively studied in the area of TBI are the cytoskeletal αII-spectrin protein and (MAP)-tau protein. αII-spectrin (280 kDa) is a major component of cell membrane cytoskeleton. Of interest, αII-spectrin is a major substrate for both calpain and caspase-3 proteases (35,43). Several *in vivo* and *in vitro* studies have provided substantial evidence indicating that αII-spectrin is processed by calpain and caspase proteases to generate signature proteolytic breakdown products indicative of necrotic and apoptotic activation after brain injury (37,44). Calpain degradation of α-II spectrin results in the appearance of two unique and highly stable α-II spectrin breakdown products of 150 kDa and 145 kDa (SBDP150 and SBDP145), which occurs early in neural cell pathology indicative of necrotic/excitotoxic neuronal cell death (Fig. 1). Similarly, caspase-3 activation results in a 150 kDa SBDP, which is further cleaved into a 120 kDa fragment (SBDP120) indicative of apoptotic neuronal cell death (Fig. 1) (43). TBI has been shown to induce calpain- and caspase-dependent degradation of structural proteins in humans and in animal models (Table I). The levels of αII-spectrin breakdown products (SBDPs) in cerebrospinal fluid (CSF) from adults with severe TBI (41 patients) were examined to assess the severity of brain injury and clinical outcome (45). Findings from this study indicated that calpain and caspase-3 increased SBDP levels in CSF were significantly increased in TBI patients at several time points after injury, compared to control subjects. Taken together these data suggest that both necrotic/oncotic and apoptotic cell death mechanisms are activated in humans following severe TBI, but with a different time course after injury. Siman et al (2004) have also examined the CSF of rats for differential protein expression in a model of mild/moderate experimental TBI employing two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) proteomic techniques. Tau protein fragment of 17 kDa, the αII-spectrin breakdown product of 150 kDa (SBDP150) and the collapsing response mediated protein-4 were increased in the CSF after the brain insult. Other proteins released in the CSF included GAP-43 and 14-3-3ζ, which are indicative of necrotic cell death whereas proteins such αII-spectrin breakdown as the products 120 kDa (SBDP120) were suggestive of apoptotic cell death (46).

In our laboratories, we have used a novel offline multidimensional separation platform termed, cation-anion exchange chromatography (CAX-PAGE/RPLC-MSMS), which is comprised of tandem ion exchange fractionation followed by 1D-PAGE separation, as a novel approach for identifying TBI biomarkers and protein breakdown products (degradomes) (32,47). We have used the CAX/neuroproteomic analysis on cortical samples obtained from rats 48 hours after a controlled cortical impact (CCI) model of experimental TBI (32). There were 59 differential protein components, of which 21 showed decreased levels and 38 showed increased levels after TBI. Among these, CRMP-2, MAP-2A/2B, and hexokinase were down-regulated whereas C-reactive protein and transferrin were up-regulated after the trauma. This work also identified novel protease substrates such as CRMP-2 and synaptotagmin,.

CRMPs are major proteins involved in neurite outgrowth and axonal guidance and alterations in their expression have been implicated in several neurological diseases including Alzheimer's, TBI, and ischemia. The CRMPs were subjected to *in vitro* calpain and caspase digestion (31). These studies allowed us to identify calpain-2, but not the caspases, as the possible proteolytic mediator of CRMP-2 breakdown following TBI.

Liu et al (2006) conducted a similar line of inquiry using high throughput immunoblotting (HTPI) technology, a novel proteomic methods for studying differential expression of proteins, in an effort to identify protease substrates for calpains and caspase-3 in an experimental TBI model (48). The authors identified 92 proteins, of which 54 were substrates sensitive to calpain-2 digestion and 38 were sensitive to caspase-3 proteolysis. This study revealed an array of proteins including β-spectrin, synaptotagmin-1, and synaptojanin-1 that are vulnerable to proteolysis following TBI (48).

Because mitochondrial dysfunction is thought to integrate various death pathways in TBI-induced neuropathology, Opii et al (2007) utilized the proteomics approach to assess potential TBI-induced changes in mitochondrial proteins in the cortex and hippocampus of rats following moderate TBI (49). Cortical and hippocampal proteins that were oxidatively modified following brain injury include pyruvate dehydrogenase and prohibitin. These data further support a role for oxidative stress as a mediator of TBI-induced brain damage (49).

In conclusion, this review indicates that many of the changes occurring in response to TBI are reflected by complex alterations in protein dynamics of relevance to protein expression, protein interaction, and protein proteolysis. These changes then are the harbinger of necrotic and apoptotic cell death in TBI models of neurodegeneration.

Methamphetamine-Induced Brain Injuries

Neuropsychiatric complications of METH addiction

Amphetamine derivatives including METH are among the most widely abused, illegal form of amphetamines, and are estimated to be abused by 25 million people worldwide. The drugs are used because they cause euphoria, hypersexuality, and increased energy (50). METH abuse is associated with a number of negative consequences, which include cognitive dysfunctions and neurological adverse events (51,52). Large doses of METH can also cause life-threatening hyperthermia, cerebrovascular hemorrhages, seizures, and death (51,53). Chronic abuse of METH is associated with withdrawal-induced depression, psychosis, and psychomotor dysfunctions (52,53). METH-induced neuropsychological abnormalities include attention deficits, memory problems, and poor decision-making (54). The accumulated evidence suggests neuropsychiatric consequences of METH abuse are related to drug-induced neuropathological changes in the brains of these METH-exposed individuals reviewed in (3).

Interestingly, METH abuse has been linked to numerous adverse neuropsychological effects showing deficits in execution memory (novel problem solving), motor skills, and episodic memory, which have been interpreted with regard to the affected dopamine rich fronto-striato-cortical loops. METH associated-episodic memory impairment is among the most susceptible cognitive functions related to METH relapse likely related to METH-induced neurotoxicity leading to brain injury. In addition, METH abusers show evidence of risky decision making and impulsivity, which has been linked to the executive aspects of working memory deficits (52,55).

Koob and colleagues investigated the effect of METH self-administration on gliogenesis in the medial prefrontal cortex (mPFC) (56). They demonstrated that daily METH self-administration (1 hour or 6 hour / day) decreased gliogenesis and increased cell death in the mPFC. Glial cells play an important role in neuronal survival and therefore a METH-induced decrease in gliogenesis might have a negative effect prefrontal cortex functioning. Schoenbaum and colleagues evaluated the effects of cocaine on orbitofrontal cortex (OFC) functioning (57). It was found that cocaine-treated rats, who demonstrated long-lasting sensitization to the locomotor activating effects of cocaine, display deficits in odor discrimination learning. Similar deficits in this task have been detected in rats with OFC lesions (58). Taken together, these studies suggest that chronic drug intake could lead to impairments in the frontal cortex which could lead to cognitive impairments and increased drug taking behavior (59).

Studies from patients suffering from either acquired brain injury to the frontal cortex or drug addictions support the link between frontal-subcortical systems injury and risk taking behaviors. Carcuel et al showed that patients with acquired frontal cortex brain injury and drug addictions share a range of neuropsychiatric dysfunctions including apathy, poor self-control, and poor executive control, as evaluated by the Frontal Systems Behavioral Scale (FrSBe). It

was shown that the addicted subjects, along with the brain injured patients, exhibited greater impairments than control subjects (60). A similar study was conducted by Lange et al, in which 104 patients with mild TBI were compared to 104 substance abuse patients (61). It was shown that there were no differences between the neuropsychological test performances of TBI patients and addicted patients on cognitive measures of visual and verbal memory and executive functioning (61). Interestingly, in one study by Regard et al, gambling behavior was evaluated in pathologic gamblers. It was shown that these "addicted" subjects had fronto-temporal neuropsychological dysfunctions and that the compulsive gambling may be a consequence of brain damage to the fronto-limbic systems (62). Based on the above studies, we argue that brain injuries due to mechanical injury and substance abuse, share similar molecular profiles and tend to increase the risk of developing addictive behavior.

Mechanisms of METH neurotoxicity

In addition to the signs and symptoms of neuropsychiatric disturbances, METH can indeed cause neurodegenerative changes in the human brain (63). These neuropathological changes include persistent decreases in the levels of dopamine transporters (DAT) in the orbitofrontal cortex, dorsolateral prefrontal cortex, and the caudate-putamen (64). They also include decreases in the density of serotonin transporters (5-HTT) in various brain regions, including the orbitofrontal and cingulate cortices of METH-dependent individuals (65). Structural magnetic resonance imaging (MRI) has documented loss of gray matter in various cortical areas (66). METH abusers also suffer from decreases in the neuronal marker, N-acetylaspartate (67) and increases in the glial marker, myoinositol (67). Microglial activation has also been reported in the brain of METH abusers using PET imaging techniques (68). In post-mortem analyses, there were decreases in dopamine (DA), tyrosine hydroxylase, and DAT levels in the basal ganglia of chronic METH users (69).

Studies in a number of animal species have replicated some of the observations obtained from clinical populations (70,71); see Cadet et al 2007 for detailed review (3). METH can cause depletion of DA, 5-HT, and their metabolites in rodents and nonhuman primates (72). METH also causes degeneration of DA and 5-HT terminals (73,74). Although the exact mechanisms involved in METH toxicity remain to be fully determined, they are similar to those reported in models of TBI, and include formation of oxidative radicals, release of glutamate, and the activation of apoptotic and necrotic death pathways (75,76).

METH neurotoxicity is thought to be mediated by the redistribution of DA from vesicular storage vesicles to the cytoplasm and extracellular space and the subsequent generation of ROS, quinine by-products, and associated lipid peroxidation of the membrane of monoaminergic terminals (77). The release of glutamate (78) and the subsequent formation of nitric oxide have also been invoked as culprits in METH-related problems (79). In addition to its toxic effects on monaminergic terminals, METH can also cause cell death via both apoptotic and necrotic mechanisms (3,71,77,80). Cell death is observed in hippocampal remnants (81), the parietal cortex (82), the striatum (83), and in several other brain regions (83).

The bases of METH-induced neuronal cell death have been extensively studied (**Table** II). METH-induced neuronal cell death is associated with activation of both ER- and mitochondria-dependent death pathways which interact to cause the ultimate demise of cells (80). Specifically, mice injected with METH showed an almost immediate activation of calcium-dependent calpain, caspase-12, increased expression of GRP78/BiP, and of C/EBP homologous protein (CHOP) which are all involved in ER stress-mediated apoptosis (80). There was also release of proteins from the mitochondria including cytochrome c and activation of caspase-9 and caspase 3. These events were followed by the proteolysis of caspase substrates such as DFF-45, lamin A and PARP in the nucleus (Fig. 1) (80). The role of the mitochondrial death pathway was also supported by the demonstration that METH is associated with

transcriptional and translational increases in the expression of pro-apoptotic Bcl-2-related genes (Bad, Bax and Bid), but decreases in the expression of Bcl-2 and Bcl-XL in the mouse cortex (84). Similar studies have been conducted in the mouse olfactory bulb where both DA depletion and death of DA neurons were reported by Deng et al (85).

The possibility of METH-induced necrotic death has been supported by some recent studies. For example, METH administration can cause the release of glutamate, which was shown to cause activate of calcium-dependent calpains via interactions with calcium permeable AMPA receptors, resulting in cleavage of their cytoskelatal substrates including αII-spectrin (86). This activation was blocked by the AMPA receptor antagonist, GYKI 52466 (86). Exposing the animals to stressful events appeared to exacerbate the effects of METH on the breakdown of spectrin (87). METH can also cause proteolysis of the neuronal cytoskelatal protein, microtubule-associated protein (MAP-tau) in the striatum, and in the hippocampus (88). MAP-tau is localized within neuronal axonal compartment and contributes to the formation of microtubule bundles that are structural elements of axonal cytoskeleton (89).

Other studies have also assessed the effects of METH on protein expression and have compared the protein breakdown products observed in TBI models (41,43). In a study from our laboratory, neurotoxicity was evaluated in rat model, 24 hrs after treatment at different concentrations (10 mg/kg-40 mg/kg). We tried to achieve a dosage paradigm similar to what is considered ‘normal acute’ or ‘binge’ use for humans (90,91). It has been shown that the 4×10 mg/kg paradigm of METH exposure in naive animals is currently the most frequently used model that mimics acute toxic dosing of METH (71). This paradigm provides excellent relevance to the intravenous and smoked METH in humans, in addition, it demonstrates the toxic effects of METH in non-tolerant users (71).

In our work, cortical and hippocampal brain regions were evaluated for the presence of cytoskelatal structural protein proteolysis as markers for necrotic and apoptotic cell death post METH injections (91). There were significant increases in the levels of products of the breakdown of αII-spectrin (SBDP120 and SBDP150) and of MAP-tau (26 kDa, 32 kDa, and 36 kDa), which are thought to be indicative of neuronal cell death processes (Fig. 1) (92,93). These breakdown products suggest that METH cause activation of the pro-apoptotic caspase-3 and the pro-necrotic calpain-1 as previously reported in TBI models (91). Immunohistochemical studies have revealed that the SBDPs were localized mainly in the axonal regions of neuronal cells localized mainly within the cortex region of the brain (90). This observed profile mimics the phenotype observed in TBI as shown in previous studies (91).

Proteomics Analysis of Methamphetamine

Proteomic analyses are now considered invaluable tools in studies attempting to elucidate the cellular and molecular underpinnings of complex biological systems (94). As such, these approaches promise to revolutionize our understanding of the effects of pharmacological agents including drugs of abuse on the brain. For example, Sokolov and Cadet have investigated the effects of chronic METH treatment on protein expression using antibody microarrays and Immunoblotting techniques (95). METH administration caused significant decreases in MEK1, Erk2p, GSK3a, and MEK7 proteins in the striata of treated mice. Interestingly, Iwazaki et al used 2D-PAGE and reported that injections of METH caused alterations in the expression of proteins, which were involved in mitochondrial functions, oxidative stress, and degenerative processes (96). Iwazaki et al have also evaluated proteomic changes following METH-induced behavioral sensitization resulting from repeated METH administration, as well as reported changes in proteins involved in apoptotic pathways (97).

In a fashion similar to our investigations of the effects of TBI, we have used the novel multidimensional proteomic platform to evaluate the proteomic changes associated with acute METH-induced neurotoxicity. We found 82 differential protein components, of which 40 were decreased and 42 were increased in abundance following acute METH treatment (47). Identified proteins belonged to pathways involved in oxidative stress, synaptic transmission, and cell death-related proteins. The relative similarities of the proteomic changes associated with both TBI and acute METH treatment (shown in Table III) suggest that there might be common neurobiological events that are involved in causing the long-term neurological and neuropsychiatric effects of these kinds of trauma. Thus, proteomic approaches, when used with appropriate classification of patient populations, hold promise to identify relevant biomarkers that might have predictive therapeutic values.

Conclusion

This review has highlighted similarities between METH-induced neurotoxicity and TBI. As discussed previously, data from Carcuel et al, Lange et al and Schoenbaum et al demonstrated the link between drug abuse and frontal-subcortical systems injury where acquired frontal injury pateints share a wide range of neuropsychiatric dysfunctions such as poor executive control (59-61). Both brain insults are coupled with neuronal injury that are mediated mainly by protease activation leading to cell death in the cortical brain region. These observations have been generated using classical and more modern molecular and proteomic approaches as shown in **Tables** I, II **and** III. When taken together, these data suggest that METH abuse can result in neurobiological consequences whose pattern can be classified as a syndrome of chemical brain injury.

Because TBI and METH-induced injuries share some neuropathological abnormalities showing elevated calpain/caspase-mediated neuronal death, it is not farfetched to also suggest that the pathological changes might play an important role in the long-term sequelae of the two syndromes. In the area of TBI, recent studies have demonstrated the use of calpain inhibitors would attenuate the progressive neuronal death and would even improve locomotor functions and reduce the functional and structural deterioration observed after experimental brain injury (98,99). The use of these pharmacological agents may hint they can be used to ameliorate the neuropsychological dysfunctions observed in these patients. In fact, a recent study by Nimmrich et al (2008) has demonstrated that the use of calpain inhibitors would attenuate NMDA-mediated neuronal injury along with associated behavioral dysfunctions (cognitive deficits) occurring after excitotoxic lesions (100). The importance of these findings is that they demonstrate the hidden link between neuronal injury and neuropsychiatric impairments observed in different types of brain injury (mechanical or drug abuse-induced). This may suggest that combating neuronal loss would lead to better psychiatric treatment (please refer to the supplement section for a detailed discussion). Finally, because TBI patients benefit from rehabilitative interventions in conjunction with the use of specific pharmacological agents (calpain inhibitors), the research discussed in the present review may be interpreted to suggest that similar treatment approaches might be beneficial to METH patients who suffer from drug-induced brain damage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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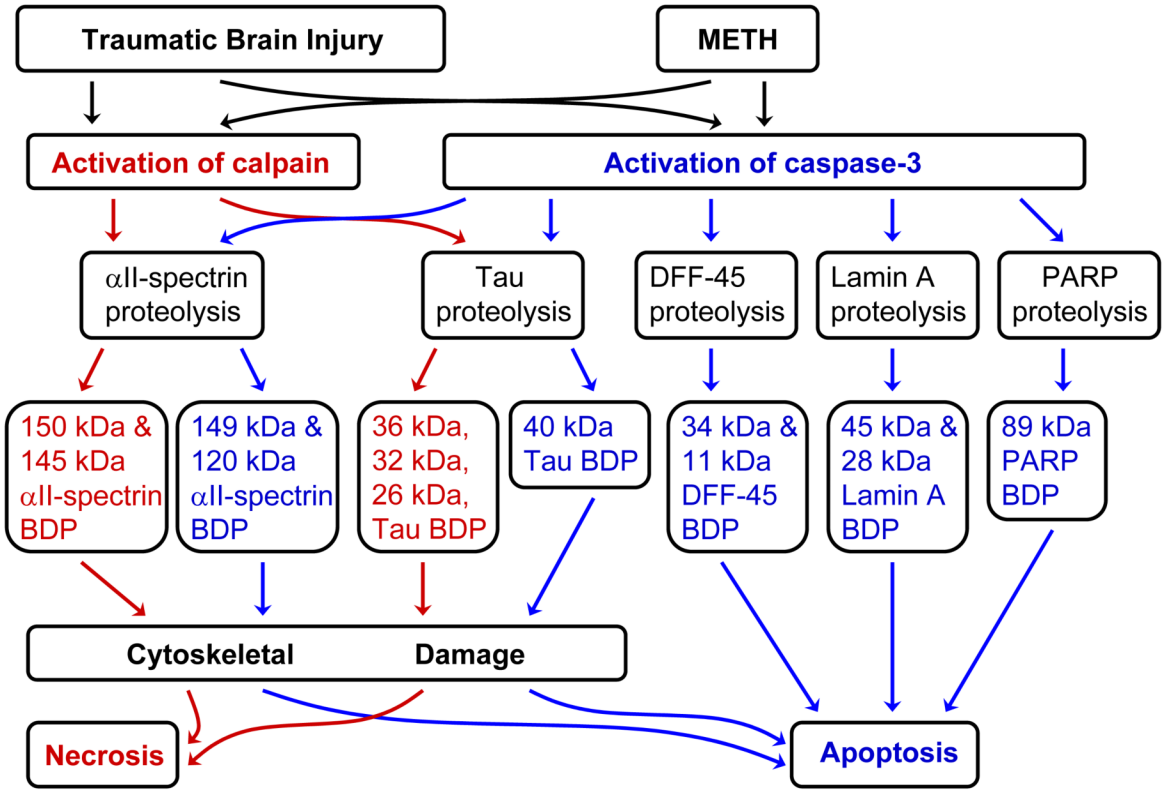

Figure 1.

Schematic diagram showing calpain (red) and caspase-3 (blue) specific proteolysis following traumatic brain injury and METH expposure. As discussed, TBI and METH exposure will induce activation of the calpain and caspase protease system that leads to the proteolysis of different cell death proteins (PARP and DFF-4) along with structural products (Tau, αII spectrin and lamin A) which will generate signature breakdown products (BDPs) indicative of the selectivitiy of either capase (blue) or calpain (red) activation.

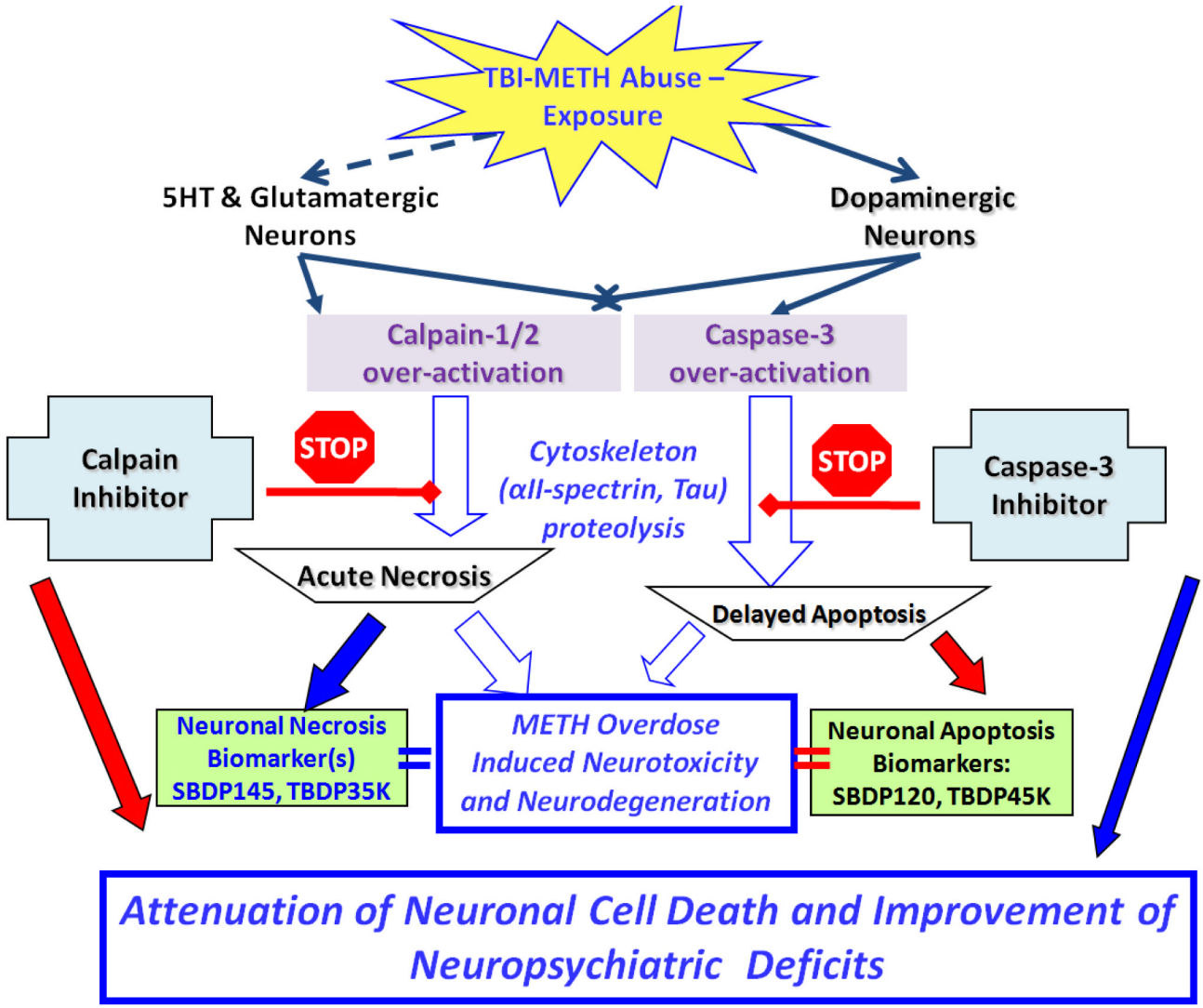

Figure 2.

TBI/METH Exposure induces neurotoxicity via two protease-dependent cell death pathways (neural necrosis and apoptosis). The use of calpain inhibitor and caspase inhibitor can provide protection against METH-induced neurotoxicity and would ameliorate the psychiatric deficits observed.

Table I

Summary of recent traumatic brain injury studies showing evidence of cytoskeletal protein degradation and cell death activation induced by calpain/caspase protease system.

TBI Model	Tissue	Proteins measured, time-points	Cellular cascades	References
Rat, controlled cortical impact (1.6 mm compression)	Cortex	↓280 kDa αII-spectrin, ↑ 120 kDa SBDP, ↓65 kDa kDa synaptotagmin, ↑37 kDa synaptotagmin BDP, ↓62 kDa CRMP-2, ↑55 kDa CRMP-2 BDP, ↑75 kDa transferrin, ↑26 kDa C-reactive protein, ↓200 kDa microtubule-associated proteins MAP2A/2B, ↓102 kDa hexokinase, ↓GAPDH 48 h after injury	Degradation of cytoskeleton-associated proteins	Kobeissy et al., (2006)
Rat, controlled cortical impact, (1.6 mm compression)	Hippocampus	↑caplpain-2 specific 145&150 kDa SBDP 110 kDa βII-spectrin BDP, 40&35 kDa striatin BDP, 33 kDa synaptotagmin-1 BDP; ↑caspase-3 specific 149&120 kDa SBDP 108&85 kDa βII-spectrin BDP, 100 kDa striatin BDP; ↑70 kDa synaptojanin-1 BDP, ↑30&25 kDa N-ethylmaleimide sensitive fusion protein BDP at 48 h after injury	Calpain-2 and caspase-3-specific proteolysis	Liu et al., (2006)
Rat, controlled cortical impact (moderate)	Cortex, hippocampus	↑protein carbonyls, ↑3-nitrotyrosine, ↑4-hydroxynonenal in the hippocampal mitochondria, ↑oxidized pyruvate dehydrogenase, voltage gated anion channel, ATP synthase, cytochrome c oxidase Va, GAPDH and prohibitin in the cortex	Oxidative damage to mitochondrial proteins, mitochondrial dysfunction	Opii et al., (2007)
Rat, controlled cortical impact (2.3 mm compression)	Cortex, hippocampus, thalamus, striatum	↑145 kDa SBDP in the cortex at 3 h-5d, hippocampus at 24 h-7 d and thalamus 15 min-14 d after injury; ↑120 kDa SBDP in the hippocampus at 15 min-6 h and striatum at 3 h-2 d following injury	Caspase-3- and calpain-dependent spectrin proteolysis	Pike et al., (1998)
Rat, controlled cortical impact moderate (2.0 mm) compression	Cortex, CSF	↓αII spectrin in the cortex, ↑αII spectrin in the CSF, ↑150 & 145 kDa SBDP in the cortex and CSF 1-3 d afterinjury	Calpain-specific αII-spectrin proteolysis	Pike et al., (2001)
Human, severe TBI, Glasgow Coma Scale score ≤8	CSF	↑145 & 150 kDa SBDP at 6 h-3 d and ↑120 kDa SBDP at 6 h-5 d following TBI	Calpain- and caspase-3-mediated αII-spectrin proteolysis	Pineda et al., (2007)
Rat, lateral fluid percussion;	CSF	↑14-3-3ζ, ↑14-3-3β, ↑αII spectrin (280 kDa),	Calpain- and caspase-dependent proteolysis	Siman et al., (2004)

TBI Model	Tissue	Proteins measured, time-points	Cellular cascades	References
mild (1.2 atm fluid pressure), moderate (2.4 atm fluid pressure)		↑150 kDa SBDP, ↑115-120 kDa SBDP at 6-24 h after injuty; ↑tau 28 kDa, ↑tau 17 kDa 48 h after injury		
Rat, controlled cortical impact, (1.6 mm compression)	Cortex, hippocampus	↑55 kDa CRMP-2 BDP, ↑58 kDa CRMP-4 BDP in the cortex at 24-48 hours, CRMP-2 BDP at hippocampus at 48 hours following injury calpain-2 treatment caused ↑55 kDa CRMP-2 BDP in naïve brain lysate,	Calpain-2-mediated CRMP-2 proteolysis	Zhang et al., (2007)
Mouse, Flat Impounder Model	Cortex	↑ 85 kDa BDP of PARP and ↓32 kDa Procaspase -3	Caspase	Hutchison et al. (2001)

Abbreviations: BDP — breakdown product, CRMP - collapsin response mediator protein, ER — endoplasmic reticulum, GAPDH - glyceraldehyde-3-phosphate hydrogenase, SBDP — αII-spectrin breakdown product, TBI — traumatic brain injury, PARP — 1Poly (ADP-ribose) polymerase-1.

Table II

Summary of recent reports studying mechanisms of cell death and altered protein dynamics induced by METH exposure.

METH treatment model	Tissue	Proteins measured, time-points	Cellular cascades	References
METH i.p. single injection, 40 mg/kg	Mouse olfactory bulb	↑cleaved caspase-3 ↑Bax, Bid protein expression (4h-24h) ↓Bcl-2 protein expression (4h-24h)	Activation of Bcl-2-dependent apoptotic pathway	Deng et al., (2007)
METH i.p. single ingection, 40 mg/kg	Mouse cortex	↑Bax, Bak, Bad, Bid mRNA (4 h-24 h) and protein levels (30 min-2 d); ↓Bcl-2, $BclX_L$, Bclw mRNA (1h -24 h) and protein levels (1h-7d)	Activation of Bcl-2 dependent apoptotic pathway	Jayanthi et al., (2001)
METH i.p. single injection, 40 mg/kg	Mouse striatum	↑cleaved caspase-12 (40 kDa) at 1h-2d, ↑cleaved caspase-9 (37 kDa) at 8h-2d, ↑cleaved caspase-3 (17 kDa) at 3h-7d ↓calpain (80 kDa) at 30 min-7d, ↑cleaved calpain (76 kDa) at 30 min-7d; ↑GRP78/ BiP mRNA (30 min-4h) and protein (8h-7d) expression, ↑CHOP/GADD153 mRNA (30 min-2h) and protein (4h-7d) expression; ↑transition of AIF, smac/DIABLO, cytochrome c from mitochondria to cytoplasm; proteolysis of DFF-45, lamin A (8h-7d), RARP (16h-2d) in nucleus	Activation of ER-dependent and mitochondria-dependent neuronal apoptosis	Jayanthi et al. (2004)
METH i.p. injections 10 mg/kg × 4, every 2h	Rat striatum	↑145 kDa SBDP at 5-7d after drug treatment, blocked by AMPA receptor antagonist, but not by NMDA receptor antagonist	Calpain-mediated, AMPA receptor-dependent spectrin proteolysis	Staszewski and Yamamoto,(2006)
METH i.p. four injections: 10 mg/kg × 2, 7.5 mg/kg and 5 mg/kg 2 h apart	Rat striatum, hippocampus	↑cleaved tau immunoreactivity in the astrocytes in striatum, CA2/ CA2 and dentate gyrus at 3d post-drug	METH-induced reactive gliosis	Straiko et al., (2007)
METH i.p. injections, 10 mg/kg × 4, every 2h	Rat striatum, hippocampus, cortex	↑cleaved tau in the striatum (3d-7d) prevented by cold ambient temperature; ↑cleaved tau in the cortex and hippocampus (3d)	METH-induced skeletal damage	Wallace et al. (2003)
METH i.p. injections, Doses 10 mg/kg × 1, 10 mg/kg × 2 or 10 mg/kg × 3, 1 h apart	Rat cortex, hippocampus	↑145 &150 kDa SBDP, ↑36, 32 & 26 kDa tau BDP in the cortex and hippocampus (24h); ↑120 kDa SBDP in the hippocampus (24h)	Calpain-dependent αII-spectrin and tau proteolysis, caspse-3-dependent αII-spectrin proteolysis	Warren et al., (2005)
METH i.p. injections, 10 mg/kg × 4, every 1h	Rat cortex	↑active calpain-1 and caspase-3 immuno-reactivity (48h) in neurons; ↑145 and 120 kDa SBDP immunoreactivity (48h) in neurons	Neuronal calpain- and caspase-mediated αII-spectrin proteolysis	Warren et al., (2007a)
METH 1 or 2 mM,	Rat primary cerebro-cortical neuronal culture	↑145 and 120 kDa SBDP,	Calpain- and	Warren et al., (2007b)

METH treatment model	Tissue	Proteins measured, time-points	Cellular cascades	References
24 & 48 h exposure		↑45, 32, 26 & 14 kDa tau BDP (24 & 48 h); ↑150 kDa SBDP (48h); calpain inhibitor caused ↓formation of 145 kDa SBDP and 14 kDa tau BDP, caspase inhibitors caused ↓levels of 120 kDa SBDP and 45 kDa tau BDP	caspse-mediated αII-spectrin and tau proteolysis	

Abbreviations: BDP — breakdown product, ER — endoplasmic reticulum, SBDP - αII-spectrin breakdown product.

Table III

Summary of major altered (upregulated and downregulated) proteins post traumatic brain injury and METH exposure identified via proteomics/biochemical approach [Ψ].

Upregulated Proteins common to TBI and METH Exposuer	Proposed functions	References
UCH-L1	Cytosolic neuronal protein involved in proteosomal regulation	Kobeissy (2006,2008)-Iwazaki (2006)
LC3	Homologue of autophagic ATG-8 protein involvedin autophagic cell death	Kobeissy (2008) -Sadasivan (2006)
MAP kinase 8	MAP kinase proteins involved in in the cortical and striatal circuits	Kobeissy (2006)- Sokolov (2006)
MAP kinase kinase 1	MAP kinase proteins involved in in the cortical and striatal circuits	Kobeissy (2006)- Sokolov (2006)
Carbonic anhydrase	Ametalloenzyme that catalyze the conversion of carbon dioxide to bicarbonate and protons,	Kobeissy (2006,2008)
Phosphoglycerate mutase 1	A glycolytic enzyme and interats with microtubles	Jenkins (2002) -Iwazaki (2008), Kobeissy (2008)
Peroxiredoxin	Cytosolic protein participates in cellular growth and metabolism	Jenkins (2002) -Iwazaki (2008)
Beta-synuclein	cytoplasmic protein involved in neuroplasticity and neurodegenerative diseases	Jenkins (2002) -Iwazaki (2008)
Gamma enolase	Cytoplasmic protein with a trophic role in synaptic remodelling	Jenkins (2002) -Kobeissy (2008)
Heat shock cognate 71	An HSP 70 family involved in ATP hydrolysis kobeissy	Jenkins (2002) -Kobeissy (2008)
Phosphoglycerate kinase 1	A major glycolytic enzyme with a transferase activity	Kobeissy(2006)-Iwazaki (2008)
Creatine kinase	Cytoplasmic protein involved in energy metabolism	Kobeissy (2006)-Iwazaki (2008)
Lactate dehydrogenase	Cytoplasmic protein involved in oxidation of lactate to produce pyruvate associated with cell death	Kobeissy (2006)- Iwazaki (2006)
Glycerdehyde-3-phosphate dehydrogenase	Glycolytic cytoplasmic enzyme involved in apoptotic cell death	Freeman (2005)- Jenkins (2002)- Kobeissy (2008)

Downregulated Proteins common to TBI and METH Exposuer	Proposed functions	References
αII - Spectrin	cytoskeletal proteins (major substrate for calpain and caspase)	Kobeissy (2006,2008)
Map-Tau	cytoskeletal proteins (major substrate for calpain and caspase)	Kobeissy (2006,2008)
CRMP-2	Neuronal axonal/dendritic guidance protein (major substrate for calpain)	Kobeissy (2006,2008)- Iwazaki (2008)
Cofilin-1	Cytoplasmic actin binding proteininvolvedin the assembly and	Jenkins (2002) -Kobeissy (2008)

Downregulated Proteins common to TBI and METH Exposuer	Proposed functions	References
	disassembly of actin filaments	
Tubulin beta chain	Cytoskeletal protein, major component of microtubules	Jenkins (2002) -Kobeissy (2008)
Pyruvate kinase isozymes	Glycolytic enzyme that catalyzes the transfer of a phosphate groups	Kobeissy (2006,2008)
Glucose-regulated protein	ER protein and stress protein facilitates protein assembly in the ER precursor (GRP 78)	Jenkins (2002) -Iwazaki (2006)
HSP-60	Mitochondrial protein involved in protein import and folding	Freeman (2005)- Jenkins (2002)-
Glutamate dehydrogenase 1	Mitochondrial matrix enzyme, with a key role in the energy homeostasis	Kobeissy (2006)- Iwazaki (2008)
Aconitase	Cytoplasmic protein with an enzymatic activity that catalyses the stereo-specific isomerization of citrate	Kobeissy (2006)- Iwazaki (2008)
α-enolase	A metalloenzyme responsible for the catalysis of 2-phosphoglycerate (2-PG) to phosphoenolpyruvate (PEP)	Kobeissy (2006)- Freeman (2005)

Ψ Protein identification was processed using different proteomic methods including 2D-DIGE, CAX-PAGE and antibody array. Protein data represent statistically significant differentially expressed proteins that were showing common trend of alteration (upregulated and downregulated) in both brain insults (METH exposure and TBI). Data were compiled from different studies as represented by the used references. Protein molecular function was derived from the Human protein Reference Database (http://www.hprd.org) and the ExPASy (**Ex**pert **P**rotein **A**nalysis **Sy**stem) proteomics server of the Swiss Institute of Bioinformatics (http://au.expasy.org/sprot/)