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Review

The Neuropathology and Neurobiology of Traumatic Brain Injury

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The acute and long-term consequences of traumatic brain injury (TBI) have received increased attention in recent years. In this Review, we discuss the neuropathology and neural mechanisms associated with TBI, drawing on findings from sports-induced TBI in athletes, in whom acute TBI damages axons and elicits both regenerative and degenerative tissue responses in the brain and in whom repeated concussions may initiate a long-term neurodegenerative process called dementia pugilistica or chronic traumatic encephalopathy (CTE). We also consider how the neuropathology and neurobiology of CTE in many ways resembles other neurodegenerative illnesses such as Alzheimer's disease, particularly with respect to mismetabolism and aggregation of tau, β-amyloid, and TDP-43. Finally, we explore how translational research in animal models of acceleration/deceleration types of injury relevant for concussion together with clinical studies employing imaging and biochemical markers may further elucidate the neurobiology of TBI and CTE.

Introduction

Head trauma with concussion is common in boxing and other contact sports, such as American football and ice hockey. It is almost 100 years since chronic brain damage in boxers, known as *punch drunk syndrome* (Martland, 1928) or *dementia pugilistica* (Millspaugh, 1937), was described. In recent years, chronic brain damage in high-profile American football players has also received increasing attention, both in the press and in the medical and scientific community. In the United States alone, about 300,000 sports-related concussions occur annually (Ellenbogen et al., 2010), and numbers are increasing worldwide (Hootman et al., 2007), and repeated concussions are thought to result in a syndrome called chronic traumatic encephalopathy (CTE). This article reviews the medical literature on mild traumatic brain injury (TBI), a term that is used interchangeably with concussion, and the chronic syndrome dementia pugilistica or CTE. We focus on findings revealed by the study of mild TBI and CTE in contact sport athletes, with the consideration that studies on the neuropathology and neurobiology in sports athletes will provide valuable insights into the neurobiological changes and mechanisms that are probably characteristic of TBI more generally.

Types of Traumatic Brain Injury

Brain injury as a result of head trauma generally falls into two categories. *Acute* brain injury comprises mild TBI or concussion including its short-term sequelae and catastrophic brain injury that may lead to death, most commonly due to subdural hematoma. *Chronic* brain injury, called dementia pugilistica or CTE, is a neurodegenerative disorder due to repeated head trauma and, in the case of professional boxers and other contact sports athletes, often starts several years after the sports career ends. We note an important distinction between amateur and professional boxing, as differences in rules have prevented TBI from being as severe a problem in the amateur version of the sport. In the next few sections, we describe the general phenomenology of these different categories of brain injury, as well as their prevalence.

Concussion

There is little agreement among medical professionals on how to define or diagnose concussion. An international consensus statement on concussion in sport defines concussion as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (Quality Standards Subcommittee, 1997; McCrory et al., 2009). Concussion causes no gross pathology, such as hemorrhage, and no abnormalities on structural brain imaging (McCrory et al., 2009). Mild concussion causes no loss of consciousness, but many other complaints such as dizziness, nausea, reduced attention and concentration, memory problems, and headache. More severe concussion also causes unconsciousness, which may be prolonged. For example, in boxing, a knockout is associated with acute brain damage due to concussion with unconsciousness. Not surprisingly, concussion occurs more often in professional boxing than in amateur boxing and other contact sports (Koh et al., 2003). The medical literature on martial arts such as kickboxing, taekwondo, and ultimate fighting is much less extensive than for boxing, but some studies have shown that the incidence of concussion per 1,000 athlete exposures is about 50 for taekwondo and 70 for kickboxing athletes (Zazryn et al., 2003; Koh and Cassidy, 2004). Concussive head impacts are also very frequent in American football. Athletes, especially linemen and linebackers, may be exposed to more than 1,000 impacts per season (Crisco et al., 2010).

Medical professionals have known for a long time that many patients who sustained minor head trauma have persistent complaints. This clinical entity is called postconcussion syndrome (PCS) and is defined as transient symptoms after brain trauma,

including headache, fatigue, anxiety, emotional lability, and cognitive problems such as impaired memory, attention, and concentration (Hall et al., 2005). Between 40%–80% of individuals exposed to mild head injury experience some PCS symptoms; most recover within days to weeks, while about 10%–15% have persistent complaints after 1 year (Hall et al., 2005; Sterr et al., 2006). In the same way, neuropsychological deficits after mild concussion or a knockout last longer than subjectively experienced or reported by boxers. Amateur boxers have measurable impairment in cognitive functioning in the days after a knockout (Bleiberg et al., 2004). Further, poor cognitive performance during a 1 month recovery period was found in professional boxers with high exposure to professional bouts (Ravdin et al., 2003). Results from a survey of 600 Japanese professional boxers indicated that 30% reported complaints after a knockout, including headache, nausea, visual disturbances, tinnitus, leg or hand weakness, and forgetfulness, that continued often days after a boxing bout (Ohhashi et al., 2002).

Catastrophic Brain Injury

Catastrophic brain injury refers to acute severe brain injury, with intracranial bleeding or cerebral contusions, that may lead to death. In boxing, about ten deaths have occurred annually during the 20th century; most were related to knockout or technical knockout (deaths due to boxing are registered in the Manuel Velazquez Boxing Fatality Collection, available at http://ejmas.com/jcs/jcsart_svinth_b_0700.htm). The most common cause of death is subdural hematoma (Guterman and Smith, 1987; Unterharnscheidt, 1995). Most deaths (about 80%) are among professional boxers, and boxing-related deaths due to brain damage occur in all rounds and in all weight classes, but somewhat surprisingly, most deaths are in lower weight classes. Deaths declined since 1983, which might be related to lower exposure to repetitive head trauma among professional boxers with shorter careers and fewer fights (Baird et al., 2010). Catastrophic brain injury also occurs in American football. During the second half of the 20th century, more than 400 players died from brain or spinal cord injury in the United States while playing (McIntosh and McCrory, 2005).

Chronic Traumatic Encephalopathy

Repetitive brain trauma may cause chronic neurological problems. For example, in 1928, Martland (1928) described chronic brain damage in boxers, which was termed punch drunk syndrome. A few years later, Millspaugh (1937) called this syndrome dementia pugilistica, which is more commonly used. Forty years ago, Corsellis et al. (1973) described neuropathological changes in a series of professional boxers with dementia pugilistica. Their key findings included neurofibrillary tangles in cortical areas, cerebellar atrophy and gliosis, hypopigmentation of the substantia nigra, and cavum septum pellucidum. Many years after these early studies documenting the histopathological changes in career boxers, it became evident that a similar chronic brain condition occurred in athletes who practiced other contact sports and had a history of repeated head trauma, and it was only recently that the first autopsy report from a football player was published (Omalu et al., 2005). Neuropathological changes were similar to those in boxers with dementia pugilistica, findings that have now been verified in larger studies (McKee et al., 2009). These authors introduced the more general term chronic traumatic encephalopathy (CTE), which has gained broader usage (Stern et al., 2011). CTE is regarded as a chronic brain syndrome due to effects of repetitive brain trauma, but there are no generally accepted guidelines for a clinical diagnosis of CTE or for how to distinguish neuropathological changes due to CTE from those due to aging and Alzheimer's disease (AD).

CTE is regarded as a neurodegenerative disorder that often occurs in midlife, years or decades after the sports career has ended (McKee et al., 2009). About one-third of CTE cases are progressive (Roberts, 1969), but clinical progression is not sequential or predictable. Clinical symptoms vary extensively, which is probably due to varying, multiple damage sites among boxers with the condition. CTE severity varies from mild complaints to severe deficits accompanied by dementia, Parkinson-like symptoms, and behavioral changes (Stiller and Weinberger, 1985; Mendez, 1995).

Clinical symptoms include neurological and cognitive complaints together with psychiatric and behavioral disturbances (Mendez, 1995; Jordan, 2000). Early neurological symptoms may include speech problems and impaired balance, while later symptoms include ataxia, spasticity, impaired coordination, and extrapyramidal symptoms, with slowness of movements and tremor (Stiller and Weinberger, 1985; Mendez, 1995; Jordan, 2000; McKee et al., 2009). Cognitive problems, such as attention deficits and memory disturbances, often become major factors in later stages of the disease (Roberts, 1969; Jordan, 2000; Guterman and Smith, 1987). Psychiatric and behavioral problems include lack of insight and judgment, disinhibition and euphoria, hypomania, irritability, and aggressiveness. The problems occur at varying times throughout the course of CTE (Roberts, 1969; Jordan, 2000; Guterman and Smith, 1987).

There are no large epidemiological studies on CTE prevalence among boxers and such a study is clearly needed. Some older studies suggest that prevalence of severe CTE in professional boxers is about 20% (Roberts, 1969; Jordan et al., 1997). It has also been suggested that around one-third of retired professional boxers have clinical symptoms, such as memory and speech disturbances, and most perform very poorly on formal cognitive tests (Casson et al., 1984). A study on professional boxers showed that 16% had complaints in daily life, e.g., headache, visual and hearing disturbances, one-sided weakness in legs or hands, shaky hands, and forgetfulness (Ohhashi et al., 2002). Furthermore, recent MRI studies show that 76% of professional boxers have abnormalities, such as hippocampal and cortical atrophy, dilated perivascular spaces, and diffuse axonal injury (DAI); these abnormalities also correlate with career length and number of bouts (Orrison et al., 2009).

In contrast, studies in amateur boxers found no change over time in neuropsychological test scores when comparing amateur boxers with long careers (25–180 bouts) and short careers (0–15 bouts) (Haglund and Persson, 1990) and no change in neuropsychological measurement results during a 9 year period (Porter, 2003). A recent meta-analysis found no strong relationship between amateur boxing and CTE (Loosemore et al., 2008). The reason for this difference between professional and amateur boxing is under debate but is probably due to the substantially lower number of rounds in amateur boxing and to the more liberal use of the referee stops contest rule to stop an

uneven bout to save the amateur boxer from a knockout. There are no available data on the prevalence of CTE among athletes active in martial arts such as kickboxing and ultimate fighting.

Biophysical Mechanisms for Brain Injury

Cerebrospinal fluid (CSF) bathes the brain and provides a protective environment. Despite this protection, blunt head injury—even without skull fracture—can damage fragile brain tissue via acceleration and deceleration forces. In the next sections, we will review the principally different types of head blows from which the force to the head is transmitted to the brain, which leads to tearing of the long axons that interconnect brain regions, and the vulnerability of the brain for repeated head trauma.

Types and Impact of Blows

There are two main principal types of head blows in boxing: (1) a straight impact to the face that generates linear acceleration of the head and (2) impact to the side of the face or from below to the chin that creates rotational acceleration (Unterharnscheidt, 1995). Studies report that head trauma, which causes linear acceleration of the brain, is relatively well tolerated, while the brain is more sensitive to angular acceleration (Cantu, 1996). Boxing punches result in proportionately more rotational than linear acceleration of the head, and a study on professional boxers verified that hook punches, which turn the head laterally with rotational acceleration of the brain, cause more concussions than parallel blows (Ohhashi et al., 2002). The opposite is true for other sports, such as football, in which the force often is directed toward the center of the head, which results in translational, or linear, acceleration (Viano et al., 2005).

Results from studies on the biomechanical forces to the head in boxing have shown that rotational acceleration of a punch is higher for the heavier weight classes, with punch severity increasing with weight class (Walilko et al., 2005). A punch from a professional boxer may generate a major force on impact, which, transferred to daily life, may be compared to being hit in the head by a 6 kg bowling ball that rolls at 20 mph (Atha et al., 1985). Indeed, many articles support the contention that boxing-related CTE is due to cumulative effects of repeated head blows. This view is, among other things, based on the knowledge that risk factors for CTE in professional boxers include a long boxing career, many bouts, high sparring exposure, many knockouts, poor performance as a boxer, and being able to tolerate many blows without being knocked out (Jordan, 2000).

Susceptibility for Repeated Trauma

Repeated blows to the head are especially detrimental for the brain, because the cerebral physiology is disturbed after mild brain trauma and concussions, which makes the brain more susceptible to further injury. Indeed, extensive animal experimental data indicate that repeated mild head injury with axonal damage increases brain vulnerability for additional concussive impacts (Barkhoudarian et al., 2011; Laurer et al., 2001). In line with these findings, American football players with a history of repeated concussions have a markedly increased risk for memory problems and cognitive impairment (Guskiewicz et al., 2005).

The cellular mechanisms for the increased susceptibility of the brain to repeated brain trauma are multifaceted. Researchers argue that metabolic dysfunction, including reduced mitochondrial energy status in the brain with increased metabolic demands but decreased energy stores with a low ATP/DTP ratio and increased lactate/pyruvate ratio, may play a role (Jenkins et al., 1989; Vespa et al., 2005; Vagnozzi et al., 2008). Yuen et al. (2009) suggested that mild trauma stimulates a type of sodium channelopathy on axons, which, in turn, intensifies pathophysiological responses to succeeding minor injuries. Longhi et al. (2005) reported that increased brain vulnerability after repeated concussions occurs via axonal damage, which is significantly amplified. In the next section, we more closely consider some of the molecular mechanisms underlying traumatic brain injury.

Neurobiological Mechanisms of Traumatic Brain Injury

There are two main categories of brain damage due to trauma: focal damage and diffuse injury. Focal injury includes cortical or subcortical contusions and lacerations, as well as intracranial bleedings (subarachnoid hemorrhage and subdural hematoma). Focal injury is due to severe direct impact on the brain and is thus mainly seen in severe cases of TBI. Diffuse injury is caused by stretching and tearing of the brain tissue and does not need any skull fracture or direct impact or crush injury to the brain surface and is therefore also seen in cases with mild TBI. The main form of diffuse injury is called diffuse axonal injury (DAI), which is due to acceleration/deceleration forces that lead to shearing of axons. In the following subsections, we discuss the neurobiology of acute mild TBI or concussion, considering how accurate this may be examined in different forms of animal models. We also review the chronic degenerative brain disorder CTE, which is found in contact sports athletes, and its similarity to other neurodegenerative disorders, especially Alzheimer's disease and Parkinson's disease (PD).

Animal Models for TBI

Animal models have been used in numerous studies to examine the neurobiology and mechanisms of TBI. Many studies exploring the neurobiology and neurochemistry of acute TBI are based on invasive animal TBI models in which the brain is exposed by craniotomy, and the cortex is subjected to injury by crush or compression, for example, by a rigid impactor (controlled cortical impact), weight drop, vacuum deformation, or by fluid percussion (for review, see O'Connor et al., 2011). These direct crush animal TBI models have been found to have a high variability in outcome, ranging from minor symptoms to fatal outcome, from a minor change in impact (Nilsson et al., 1990), which might limit their utility as models of human mild TBI. Animal TBI models based on acceleration/deceleration of the skull and brain that replicate the dynamics of damage due to rotational forces leading to diffuse brain injury have been difficult to develop, due to the lower mass of the animal brain (O'Connor et al., 2011; Johnson et al., 2012). The vast majority of people with sports-related brain trauma have mild TBI with concussion, without skull fracture or neuroimaging evidence of contusions or bleedings due to direct crush injury to the brain (Alexander, 1995; McCrory et al., 2009). Instead, these athletes have subconcussive or concussive impact to the brain, due to

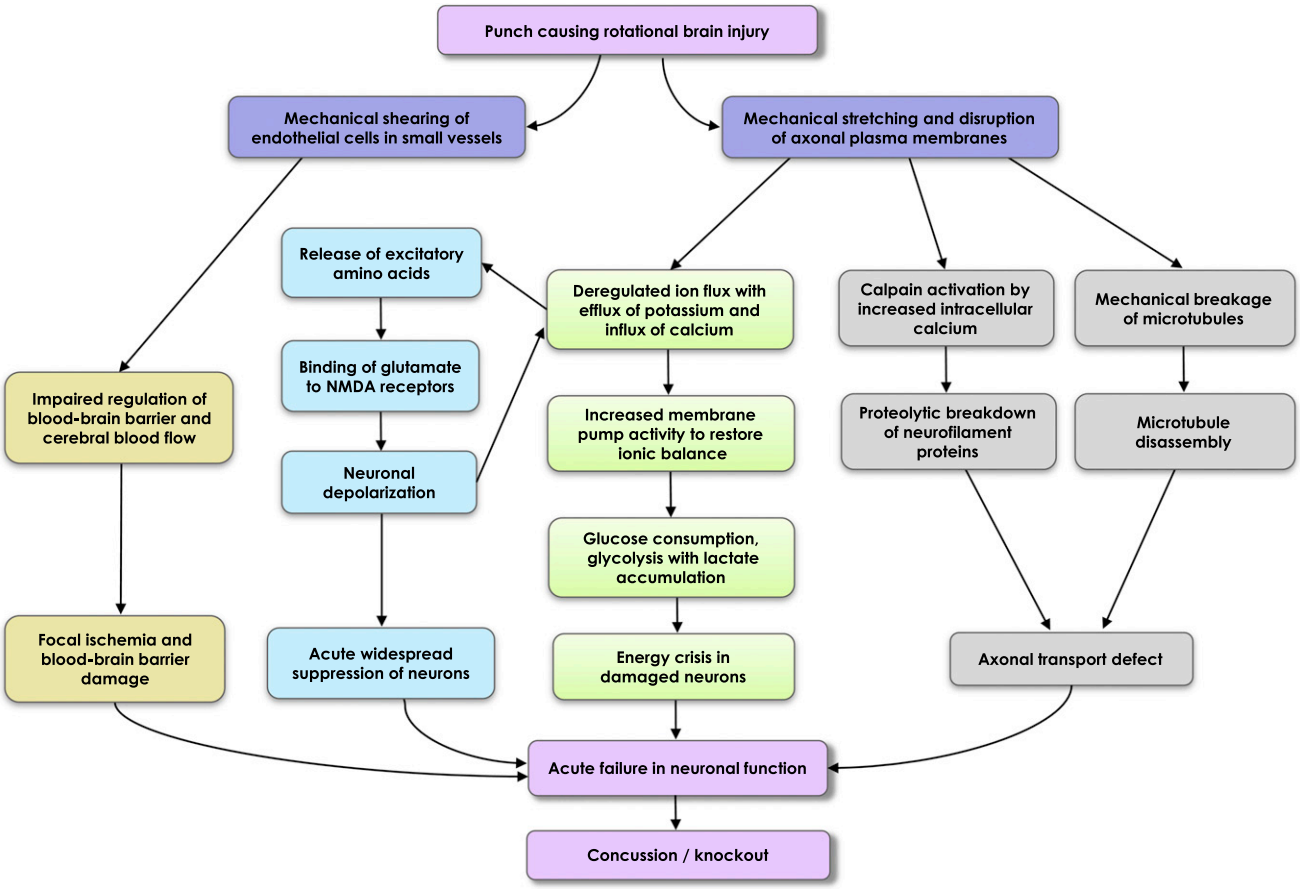

Figure 1. Molecular Pathophysiology of Concussion
A schematic flow chart of the molecular changes after rotational head injury that leads to concussion and knockout with loss of consciousness. Abbreviations: NMDA, *N*-methyl-D-aspartate.

acceleration/deceleration forces with diffuse axonal injury. For this reason, it is questionable whether animal models based on direct crush or compression injury are relevant models to study the neurobiology of mild TBI.

Acute Cellular and Neurochemical Effects of TBI

Closed head injury with acceleration and deceleration forces to the brain causes a multifaceted cascade of neurochemical changes that affect brain function (see Figure 1). Although detailed understanding of the pathophysiology of concussion is lacking, studies using the mild fluid percussion model support the idea that the initiating event is stretching and disrupting of neuronal and axonal cell membranes, while cell bodies and myelin sheaths are less affected (Spain et al., 2010). Resulting membrane defects cause a deregulated flux of ions, including an efflux of potassium and influx of calcium. These events precipitate enhanced release of excitatory neurotransmitters, particularly glutamate. Binding glutamate to *N*-methyl-D-aspartate (NMDA) receptors results in further depolarization, influx of calcium ions, and widespread suppression of neurons with glucose hypometabolism (Giza and Hovda, 2001; Barkhoudarian et al., 2011). Increased activity in membrane pumps (to restore ionic balance) raises glucose consumption, depletes energy stores, causes calcium influx into mitochondria, and impairs oxidative metabolism and consequently anaerobic glycolysis with lactate production, which might cause acidosis and edema (Giza and Hovda, 2001; Barkhoudarian et al., 2011).

Diffuse Axonal Injury

DAI, caused by shearing of fragile axons by acceleration/deceleration forces from the trauma, is the primary neuropathology of TBI (Adams et al., 1989; Alexander, 1995; Meythaler et al., 2001; Johnson et al., 2012). DAI is present also in patients with mild TBI (Oppenheimer, 1968), and the severity of DAI is proportional to the deceleration force (Elson and Ward, 1994). In patients with TBI, DAI is notoriously difficult to identify using CT and conventional MRI, although MRI is more sensitive (Kim and Gean, 2011). However, novel MRI techniques such as diffusion tensor imaging (DTI) have been shown to be useful to asses axonal integrity and to identify DAI in patients with mild TBI (Bazarian et al., 2007; Mayer et al., 2010; Miles et al., 2008) and also in athletes with mild sports-related concussive or subconcussive TBI (Bazarian et al., 2012).

By histological techniques, DAI can be identified very early (hours) after trauma and is characterized by sequential changes with an acute shearing of axons, which leads to disrupted axonal

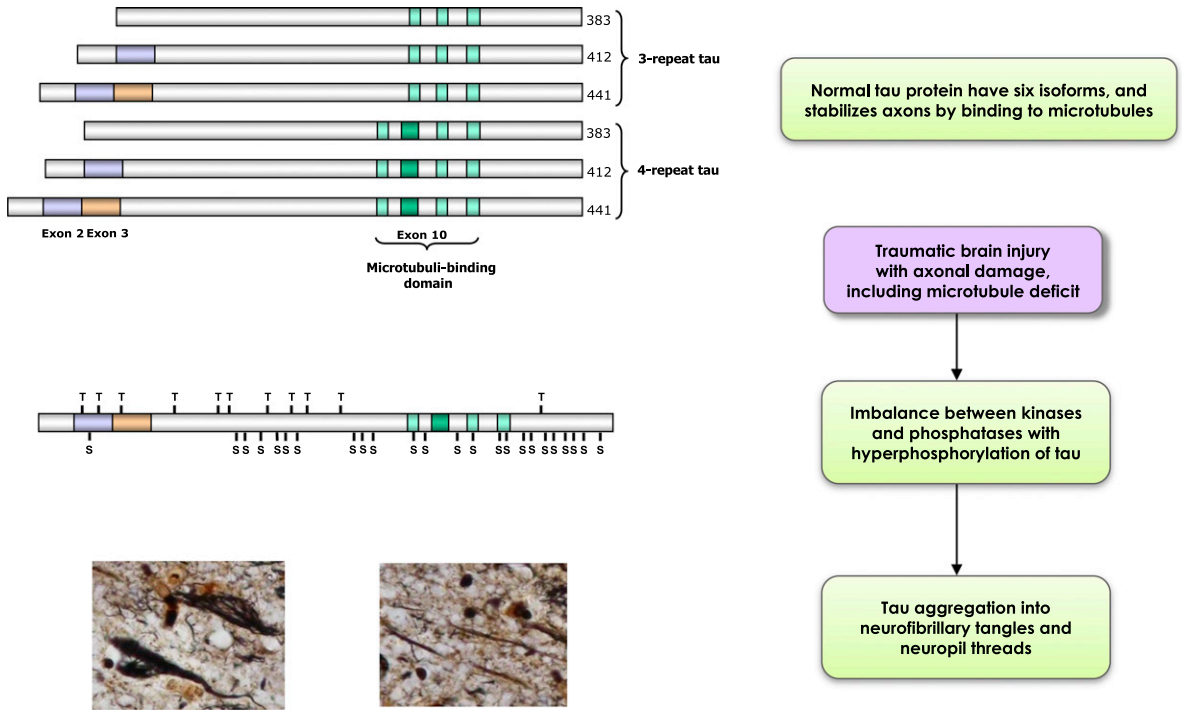

Figure 2. The Tau Pathway and Tau Pathology in CTE

Schematic flow chart of the molecular changes related to tau phosphorylation and aggregation in repeated mild traumatic brain injury (TBI). Tau is a protein located in the neuronal axons that, by binding to the microtubules through its microtubule-binding domains, promotes microtubule assembly and stability. Tau has six isoforms that contain either three or four microtubule-binding domains and several phosphorylation sites, either threonine (T) or serine (S). Through mechanisms which are unknown, TBI causes an imbalance in kinases and phosphates, which results in tau phosphorylation. Hyperphosphorylation of tau makes it prone to aggregation into insoluble fibrils (paired helical filaments, PHF) and larger aggregates in the form of neurofibrillary tangles and neuropil threads.

transport with axonal swellings and thereafter secondary disconnection and in the end Wallerian degeneration (Johnson et al., 2012). DAI with axolemmal disruption causes calcium influx, neurofilament compaction, and microtubule disassembly. Neurofilament compaction is an early event caused by calpain-mediated proteolysis of neurofilament side arms or phosphorylation. Calcium influx triggers microtubule disassembly (Giza and Hovda, 2001; Barkhoudarian et al., 2011). Cytoskeletal pathology may have several mediators. In animal trauma models of axonal pathology, calcium homeostasis disruption results in calpain-mediated proteolytic degradation of essential cytoskeletal proteins, such as neurofilament proteins. Calcium homeostasis is the primary regulator of calpain activation; disruption leads to increased intracellular-free calcium (McCracken et al., 1999; McGinn et al., 2009; Saatman et al., 2010).

Microtubule disorganization may be a direct effect of dynamic axon stretching. Ultrastructural analysis of axons displays immediate breakage and buckling of microtubules postinjury, which triggers progressive microtubule disassembly (Tang-Schomer et al., 2010). This results in accumulation of organelles that are transported in the axon, and axonal swelling called axonal retraction balls, with eventual disconnection and axotomy (Giza and Hovda, 2001; Barkhoudarian et al., 2011). Neuronal damage with axonal bulbs and swellings is most commonly located in the cortical sulci at the interface between gray and white matter (Chen et al., 2004). MRI studies that use DTI show that the extent of DAI after mild TBI is related to postconcussion cognitive problems (Lipton et al., 2008; Niogi et al., 2008; Wilde et al., 2008).

Tau Pathology and Tangle Formation

As early as the 1970s, Corsellis et al. (1973) reported neurofibrillary tangles in neocortical areas in boxers with CTE. Several studies have since confirmed these findings of extensive tangle pathology in postmortem studies (Dale et al., 1991; Tokuda et al., 1991; Schmidt et al., 2001; Hof et al., 1992; Geddes et al., 1996). In addition to neurofibrillary tangles, neuropil treads and glial tangles are also elements of CTE (McKee et al., 2009).

Cortical tangles also constitute a key component of Alzheimer's disease. But because they are found in many chronic neurological diseases (Wisniewski et al., 1979) with different etiology, it is possible that they represent a more general response to neurodegenerative pathology. Indeed, their abundance in CTE, which is caused by repeated brain trauma episodes, further supports that they may represent a response to brain damage. Tangles are found intracellularly in the cytoplasm of neurons and consist of thread-like aggregates of hyperphosphorylated tau protein (Grundke-Iqbal et al., 1986). Tau is a normal axonal protein that binds to microtubules via its microtubule-binding domains, thus promoting microtubule assembly and stability. There are six different isoforms of tau, each containing several serine or threonine residues that can be phosphorylated. In AD, tau is frequently found in a hyperphosphorylated form (Figure 2). Such tau phosphorylation reduces microtubule binding, which causes disassembly of microtubules

and thus impaired axonal transport, leading to compromised neuronal and synaptic function, increased propensity of tau aggregation, and subsequent formation of insoluble fibrils and tangles (Mandelkow and Mandelkow, 2012). In aggregate, these cellular and molecular changes further compromise neuronal function.

Tangles in boxers with dementia pugilistica/CTE are structurally and chemically similar to those found in AD, in which CTE tangles also consist of hyperphosphorylated and ubiquitinated tau (Dale et al., 1991; Tokuda et al., 1991). Hyperphosphorylated tau from dementia pugilistica and AD brains is phosphorylated at the same amino acids, including the AT8 epitope, contains all six tau isoforms, and shows the same relation between 3- and 4-repeat tau (Schmidt et al., 2001) (Figure 2). However, it should be noted that the tangles are found in different populations of cortical pyramidal neurons; in dementia pugilistica/CTE, tangles are found in the superficial neocortical layers, while tangles in AD are found in deep and in superficial layers (Corsellis et al., 1973; Hof et al., 1992; McKee et al., 2009). Furthermore, tau pathology in CTE is patchy and irregularly distributed, possibly related to the many different directions of shearing forces induced by physical trauma (McKee et al., 2009).

Experimental studies in animals suggest that intra-axonal tau accumulation and tau phosphorylation may be consequences of repeated brain trauma. Controlled brain trauma in animal models has been shown to increase tau immunoreactivity and tau phosphorylation in the perinuclear cytoplasm and in elongated neuritis (Tran et al., 2011). These abnormalities correlate with injury severity (Tran et al., 2011). Studies on brain trauma induced by rotational acceleration in experimental animals show an accumulation of both tau and neurofilament proteins in damaged axons (Smith et al., 1999). Treatment with γ-secretase inhibitors mitigates amyloid pathology but does not affect TBI-induced tangle formation, suggesting that TBI-induced tau pathology is not a downstream event of Aβ accumulation and plaque formation (Tran et al., 2011). The neurochemical disturbances that trigger tau pathology in CTE are not known in detail, but recent studies show that TBI induces an abnormal intra-axonal activation and accumulation in kinases that can phosphorylate tau (Tran et al., 2012). The kinase c-Jun N-terminal kinase (JNK) is markedly activated in damaged axons, and inhibition of JNK activity was found to reduce the accumulation of both total and phosphorylated tau in injured axons (Tran et al., 2012).

APP and Aβ Generation with Plaque Formation

After identification of Aβ as the key component of plaques in AD, Roberts et al. (1990) re-examined brains from the classic Corsellis report (Corsellis et al., 1973) to determine whether Aβ pathology may also be a key histopathological characteristic in dementia pugilistica. Here, the authors demonstrated that all brains from boxers with substantial tangle formation also had extensive Aβ deposits consisting of diffuse plaques (Roberts et al., 1990). The intensity of Aβ plaque deposition was comparable to that found in AD cases (Roberts et al., 1990). The presence of Aβ plaques after acute severe brain trauma was verified in many reports, including studies on fresh surgically excised brain tissue samples (Roberts et al., 1994; Ikonomovic et al., 2004).

Aggregation of Aβ and plaque formation constitutes central elements of AD. Aβ is generated from amyloid precursor protein (APP) by the concerted action of β-secretase and γ-secretase (Blennow et al., 2006). β-Secretase was identified as β-site APP-cleaving enzyme 1 (BACE1), while γ-secretase consists of a complex with four components that include presenilin, nicastrin, Pen-2, and Aph-1. Presenilin is present in the active site of the γ-secretase complex (Blennow et al., 2006). Expression of APP is highest in neurons and, under normal conditions, APP (Koo et al., 1990; Ferreira et al., 1993; Kamal et al., 2000), β-secretase (BACE1) and γ-secretase (presenilin) (Sheng et al., 2003) are translocated by axonal transport to the synapses, where APP can be cleaved by the secretases, thus generating Aβ (Kamal et al., 2001).

Extensive research contends that APP has neurotrophic functions, including promotion of axonal sprouting, neurite outgrowth, and synaptogenesis, which are important for neuronal survival after axonal damage (Small, 1998; Small et al., 1999; Alvarez et al., 1992; Xie et al., 2003). APP is upregulated in response to brain trauma and administration of soluble α-secretase-cleaved APP improves functional outcome and reduces neuronal cell loss and axonal injury after experimental TBI in animals (Thornton et al., 2006).

Studies on human brain tissue samples have demonstrated that APP accumulates in neurons and axons after brain trauma with axonal damage (McKenzie et al., 1994; Sherriff et al., 1994; Gentleman et al., 1995; Ahlgren et al., 1996; Gleckman et al., 1999). Postmortem studies on human brain tissue samples from patients who sustained mild TBI but died of other causes have shown that this APP accumulation occurs very rapidly (within a few hours) after brain trauma and is present in cases with mild trauma (Blumbergs et al., 1994; McKenzie et al., 1996; Johnson et al., 2012). Besides APP, acute intra-axonal Aβ accumulation is a prevalent trait in human TBI (Smith et al., 2003; Uryu et al., 2007; Chen et al., 2009). Release of β-amyloid (especially Aβ42) into tissue and plaque formation around damaged axons occurs after APP accumulation and β-amyloid production in damaged axons (Roberts et al., 1991; Graham et al., 1995; Horsburgh et al., 2000a; Smith et al., 2003).

Studies on brain trauma induced by rotational acceleration in animal experiments show an accumulation of APP and Aβ within damaged axons throughout the white matter, which in a subset of animals is accompanied by Aβ diffuse plaques (Smith et al., 1999; Li et al., 2010; Tran et al., 2011). After TBI, APP accumulation, BACE1 and presenilin enzymes, and the Aβ product all accumulate in the terminal bulbs of disconnected axons and in a limited number of neurons in cortical areas (Chen et al., 2004).

Experiments in AD transgenic mouse models suggest that the degree of intra-axonal APP and Aβ accumulation correlates with injury severity (Tran et al., 2011) and that repetitive mild TBI increases Aβ deposition (Uryu et al., 2002). Appearance of Aβ accumulations was consistent with the morphology of injured axons. Essentially all axonal Aβ deposits were also positive for APP and for neurofilament light protein, which is a well-established marker for axonal damage (Tran et al., 2011). Intra-axonal APP accumulation is an established marker for DAI and is the gold standard to identify DAI in routine forensic medicine, for example, in deaths from motor vehicle accidents and suspected

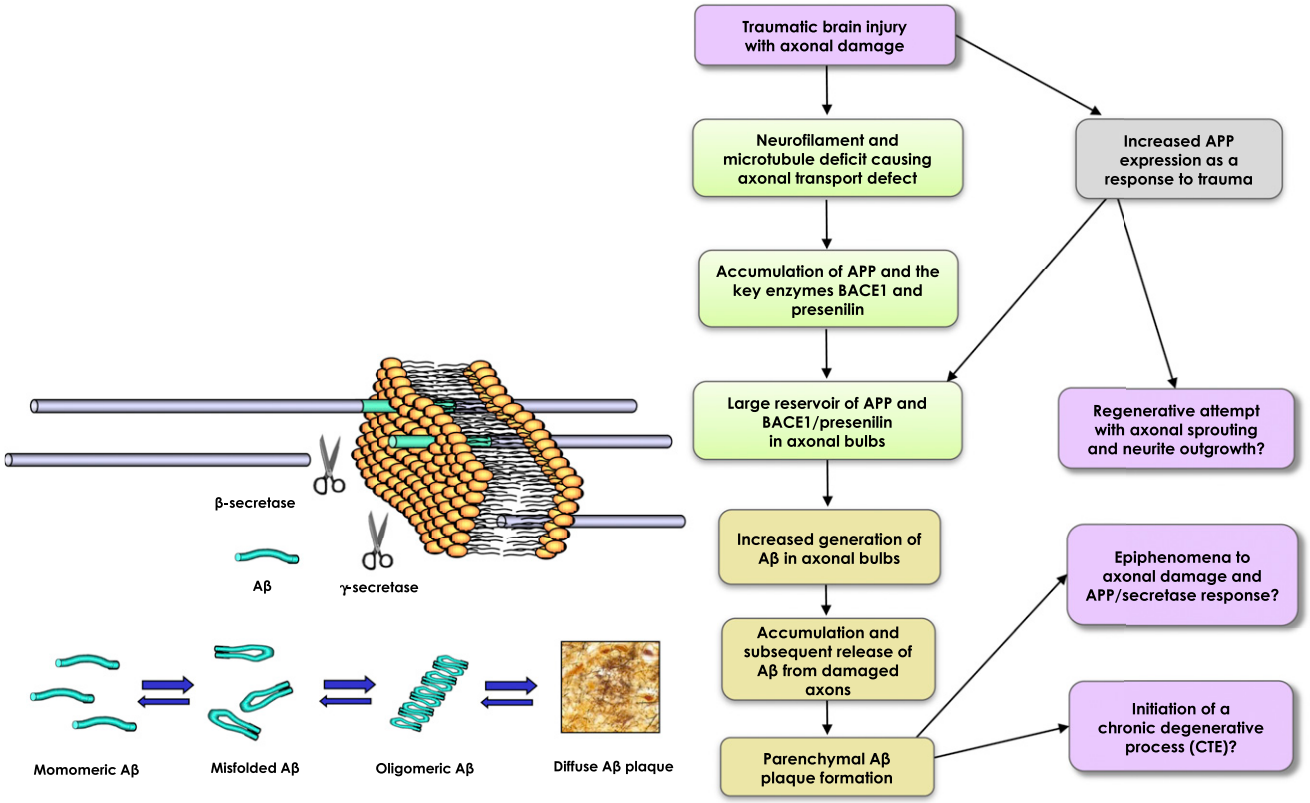

Figure 3. Neurochemical Pathophysiology of APP and Aβ in CTE

Schematic flow chart of the molecular changes in APP and Aβ metabolism after repeated mild traumatic brain injury (TBI). Traumatic brain injury initiates a process resulting in parenchymal deposits of Aβ, mainly in the form of diffuse plaques. A large body of data support that the increase in APP is part of a regenerative response to trauma, while it is debated whether the increase in Aβ with aggregation and plaque formation may initiate a chronic degenerative process, or whether it is simply an epiphenomena to neuronal damage. Abbreviations: APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme 1; CTE, chronic traumatic encephalopathy.

shaken baby syndrome (Gleckman et al., 1999; Gorrie et al., 2002). The increase in APP expression after DAI is probably related to the proposed role of APP for promoting axonal outgrowth after injury (Chen and Tang, 2006).

Data from studies of brain trauma in humans and on experimental rotational brain trauma in animals indicate that DAI is a long-term process in which axons continue to degenerate and swell during an extended period. In the disconnected axons, both the substrate (APP) and the key enzymes (BACE1 and presenilin) for Aβ generation accumulate in the swollen axonal bulbs, which may lead to abnormal APP metabolism (Chen et al., 2004). Furthermore, this large intra-axonal APP reservoir and canonical enzymes for Aβ generation may result in abnormal Aβ overproduction and accumulation. Peptide aggregation in axonal bulbs follows Aβ overproduction. After Aβ expulsion from injured axons, accumulation occurs in the extracellular space as diffuse plaques (Chen et al., 2004; see Figure 3).

Other Types of Possible Pathogenic Changes

Microglial Activation. Microglial cells play an important role in the immune system in the brain and are key mediators of the inflammatory response after TBI. Experiments in animal TBI models show that microglia rapidly migrate toward lesioned tissue, and activated microglia form extended cytoplasmic processes in direct contact with injured axons to form a potential barrier between the healthy and injured tissue, suggesting that microglial activation is a response to the axonal damage (Davalos et al., 2005; Shitaka et al., 2011). This microglial response is associated with an upregulation of both pro- and anti-inflammatory genes, chemokines and other inflammatory mediators (Ziebell and Morganti-Kossmann, 2010). However, it is not settled whether modulation of this inflammatory response to brain trauma may have any therapeutic effects; on the one hand, pharmacological reduction of microglial activation might reduce inflammation and improve neuronal survival, but on the other hand, microglial activation might stimulate axonal regeneration after injury (Loane and Byrnes, 2010).

Regenerative Phenomena. Similar to other types of injury, TBI seems to elicit a plasticity regenerative response that includes dendritic and synaptic sprouting with increased dendritic arborization and synaptogenesis (for review, see Keyvani and Schallert, 2002). While it is beyond the scope of this Review to go into detail on the complex pattern of protein changes controlling this regenerative response, it is worth briefly mentioning that alterations in transcription factors c-Jun and ATF-3 have been reported in TBI, suggesting that such factors may be important in axonal regeneration after DAI (Greer et al., 2011). Furthermore,

structural proteins such as adhesion molecules and growth proteins, including growth-associated protein GAP-43, have also been implicated in neurite sprouting of disconnected damaged axons after the acute phase of TBI (Christman et al., 1997).

TDP-43 Pathology. Other proteins that may be involved in CTE pathogenesis include the transactivation responsive region deoxyribonucleic acid-binding protein 43 (called TAR DNA-binding protein 43 or TDP-43). Intraneuronal TDP-43 accumulation was initially considered a disease-specific aspect of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and amyotrophic lateral sclerosis (ALS) (Neumann et al., 2006). Later studies have found that accumulation of TDP-43 is a feature of other neurodegenerative diseases as well, such as AD and dementia with Lewy bodies (Kadokura et al., 2009; King et al., 2010) and several other diseases.

Recent studies have also shown that the widespread accumulation of TDP-43 occurs in boxers and American football players with CTE after repeated brain trauma in several gray matter structures, e.g., brainstem, basal ganglia cortical areas, and subcortical white matter (King et al., 2010; McKee et al., 2010). TDP-43 accumulations in chronic neurodegenerative diseases contain phosphorylated TDP-43 (Neumann et al., 2009). A study using phosphorylation-dependent antibodies showed intraneuronal accumulation of nonphosphorylated, but not phosphorylated, TDP-43 after single TBI (Johnson et al., 2011). Animal experiments suggest that axonal damage results in an upregulation of TDP-43 expression together with a redistribution of TDP-43 from the nuclear compartment to the cytoplasm (Moisse et al., 2009; Sato et al., 2009). Taken together, these data suggest that TDP-43 accumulation in CTE and after TBI may be part of a physiological injury response (Johnson et al., 2011).

Lack of α-Synuclein Pathology. Parkinsonism may be associated with CTE in boxers, for which the term pugilistic parkinsonism has been used. Some studies reported loss of neurons in the substantia nigra in boxers with CTE (Corsellis et al., 1973), similar to that found in Parkinson's disease. However, neuronal loss in athletes with CTE is observed in the absence of Lewy bodies and the accumulation of α-synuclein, which is the main component of Lewy body pathology seen in PD (McKee et al., 2009).

APOE and Genetic Susceptibility to CTE

Apolipoprotein E (ApoE) was originally identified as a main component of lipoproteins in plasma and has important functions in cholesterol and lipid transport. Peripheral ApoE is synthesized in the liver, but expression is also high in the CNS, where ApoE is the dominant apolipoprotein, primarily synthesized by astrocytes, although neurons and microglia also may contribute to its production (Huang et al., 2004). Both animal experiments and clinical studies in man have shown that after brain injury, large amounts of membrane lipids are released from the damaged axons, and in response astrocytes increase ApoE expression, with release of ApoE to the extracellular space to scavenge cholesterol and other lipids for reuse during axonal and synaptic regeneration (Poirier et al., 1991, 1993; Horsburgh et al., 2000b). Taken together, numerous studies suggest a central role for ApoE in lipid delivery for growth and regeneration of axons after neuronal injury.

The *APOE* gene has three alleles (*APOE* ε2, *APOE* ε3, and *APOE* ε4). *APOE* ε3 is the most common in the population. Solid scientific evidence shows that the *APOE* ε4 allele is a strong susceptibility gene for AD (Roses, 1996). Similarly, Jordan et al. (1997) reported that high-exposure boxers with the *APOE* ε4 allele were at increased risk of CTE compared to high-exposure boxers without the *APOE* ε4 allele. All severely impaired boxers had at least one *APOE* ε4 allele. This finding suggests that risk of CTE after brain injury may be genetically determined. In agreement, a meta-analysis of 14 cohort studies showed that the *APOE* ε4 allele is associated with poor long-term outcome after TBI, although it does not affect initial severity of the brain injury (Zhou et al., 2008).

The mechanism for the association between the *APOE* ε4 allele and poor outcome after TBI remains controversial. As reviewed above, ApoE is a key mediator of cholesterol and lipid transport in the brain and plays a crucial role in repair of damaged axons after trauma (Poirier, 1994). A series of studies demonstrated that *APOE* knockout neurons show defective neurite sprouting, which can be restored by ApoE3 but not ApoE4 lipoproteins (Teter et al., 1999) and that increased ApoE4 expression reduces neuronal sprouting (Teter et al., 2002). These findings suggest that the negative effect of ApoE4 on neuronal sprouting is a gain of negative activity. In the human brain, the *APOE* ε4 dose correlated inversely with dendritic spine density in the hippocampus in AD patients and cognitively normal older persons (Ji et al., 2003). Experiments in the human *APOE*-targeted replacement mouse model show decreased spine density and a marked impairment in reactive neuronal sprouting and synaptogenesis in human *APOE* ε4 mice compared to *APOE* ε3 mice, despite similar increases in ApoE expression levels (White et al., 2001; Blain et al., 2006; Dumanis et al., 2009). These data suggest that *APOE* ε4 may act via impaired neuronal regeneration after brain insults. Another line of evidence links the *APOE* ε4 allele with Aβ generation and plaque formation. Severe TBI in humans induces cortical Aβ deposition in about 30%–50% of patients (Roberts et al., 1991). Further studies showed that the *APOE* ε4 allele is clearly overrepresented in trauma patients who display Aβ deposition (Nicoll et al., 1995, 1996). In a study on AD transgenic mice exposed to TBI, mice coexpressing ApoE4 showed greater Aβ deposition than ApoE3 mice and the presence of thioflavine-S-positive Aβ plaques (Hartman et al., 2002). These data suggest that ApoE4 may trigger Aβ deposition and plaque formation as part of an acute phase response to brain injury.

Based on the association between poor neurological long-term outcome in carriers of the *APOE* ε4 allele after severe TBI (Zhou et al., 2008) and findings suggesting that boxers with the *APOE* ε4 allele suffer from more severe CTE (Jordan et al., 1997), medical professionals have raised the issue of providing genetic counseling for athletes. However, overall, these findings should be interpreted with some caution, as a large prospective study found no overall association between *APOE* genotype and 6 month outcome after TBI, except that the *APOE* ε4 allele reduced the likelihood of a favorable outcome in children and young adults (Teasdale et al., 2005). Furthermore, in the meta-analysis of study on the effect of the *APOE* ε4 allele long-term outcome after severe TBI (Zhou et al., 2008), the relative risk

for unfavorable outcome was reported to be 1.36, which is relatively minor. So apart from ethical issues linked to counseling, further studies are needed before such an approach could be considered valuable from a preventative or clinical standpoint.

Monitoring TBI Using Biomarkers

Currently, no imaging or biochemical measurements exist for objectively identifying or quantifying whether or not an individual has axonal damage or other types of brain injury. CSF is in direct contact with the extracellular space of the brain, and thus biochemical changes in the brain are reflected in CSF. Increased CSF levels of biomarkers for axonal damage (e.g., tau and neurofilament light [NFL] protein) and glial cell damage (e.g., glial fibrillary acidic protein [GFAP] and S-100β) are found after acute brain damage due to stroke and encephalitis (Hesse et al., 2000; Nylén et al., 2006; Petzold et al., 2008). The degree of increase of these biomarkers in CSF correlates with severity of acute brain damage (Hesse et al., 2000; Nylén et al., 2006; Petzold et al., 2008).

In a longitudinal study on amateur boxers, a pronounced increase was found in the CSF level of NFL protein after a bout (Zetterberg et al., 2006). The degree of increase in CSF NFL also correlated with number and severity of received head blows. CSF NFL returned toward normal levels after a 3 month rest (Zetterberg et al., 2006). Similar but less pronounced changes were found for CSF T-tau. The finding of an increase in CSF NFL that correlates with severity of the bout in amateur boxers has recently been verified in a larger, independent study (Neselius et al., 2012).

NFL and tau are important constituents of neuronal axons, and the CSF level of these proteins may serve as biomarkers for axonal damage and degeneration (Grady et al., 1993; Olsson et al., 2011). Increases in CSF NFL and T-tau in boxers most likely reflect damage to neuronal axons from hits to the head. In agreement with this interpretation, a marked increase in CSF T-tau, which also correlates with a 1 year outcome, is found after severe TBI (Franz et al., 2003; Öst et al., 2006), and high CSF NFL levels are found in patients with nerve tissue damage after spinal cord injury (Guéz et al., 2003).

These findings bring promise that CSF biomarkers may be used for diagnostic and prognostic counseling of athletes. Post-injury levels may give information on the severity of axonal damage after a knockout, and longitudinal follow-up samples may be used to monitor whether an increase in axonal proteins have subsided and when it may be suitable for athletes to resume sparring and competitions. However, due to its invasive nature, lumbar puncture may be difficult to introduce on a routine basis in athletes. Analysis of biomarkers for brain damage in blood samples may thus be preferable. An increase in serum levels of neuron-specific enolase (NSE), a biomarker for neuronal damage, was found in amateur boxers, even after an extended resting period (Zetterberg et al., 2009), which suggests that repetitive head trauma in boxers results in sustained release of brain-specific protein to the peripheral circulation (Zetterberg et al., 2009). Similarly, an increase in NSE, and also the glial cell biomarker S-100β, was found in serum in amateur boxers who received direct punches to the head compared with boxers who received body punches but blocked and parried head punches (Graham et al., 2011).

Future Prospects

As reviewed in this paper, knowledge on the neurobiology and pathogenesis of contact sports-related mild TBI/concussion and CTE is limited, and there is no treatment available. Another risk group for CTE is military veterans who have been exposed to repeated blast injury by firing heavy weapons or other types of explosions. A recent study showed that militaries exposed for blast injury may develop CTE with tau-linked pathology similar to that found in some contact sport athletes (Goldstein et al., 2012). Thus, there is a need of large longitudinal clinical multicenter studies in military personnel exposed to blasts and athletes involved in contact sports at risk for single or repeated mild TBI. Such studies are needed to determine the incidence and prevalence of concussion and CTE and to improve our understanding of the relationship between repetitive acute brain damage and its long-term sequelae.

Furthermore, there are no generally accepted guidelines for a clinical diagnosis of CTE and no established biomarkers to assist the clinician. For this reason, longitudinal clinical studies employing biomarkers (MRI measures, PET imaging, and CSF biochemical markers) in a similar manner to what has been done in the U.S. Alzheimer's disease neuroimaging initiative study (Weiner et al., 2012) would be of importance. Such studies could serve as the basis to develop novel biomarker-based clinical consensus criteria for CTE and would also increase knowledge on pathogenic mechanisms and the temporal evolution of different forms of pathology.

In a similar way, despite the increasing number of neuropathological studies on CTE, there are no generally accepted criteria for how to distinguish neuropathological changes found in CTE from those due to aging and AD. In addition, it is not established whether there are differences in neuropathology between CTE in American football players, with predominance of tau pathology (McKee et al., 2009; Omalu et al., 2011) and dementia pugilistica in boxers, with marked β-amyloid deposition and diffuse plaques in addition to tau pathology (Roberts et al., 1990; Tokuda et al., 1991). Longitudinal clinical studies with neuropathological follow-up would serve to resolve these questions.

Experimental studies in animal models based on acceleration/deceleration forces to the brain, which resemble the human situation in mild TBI, will also be important to further explore the complex neurochemical and neurobiological changes after acute TBI. Knowledge on TBI neurobiology would benefit if data from such animal studies would be verified in clinical studies employing molecular biomarkers as well as in neuropathological studies. Further, as reviewed above, the neurobiology of CTE resembles that in AD. In mild TBI, axonal damage with DAI triggers a series of neurobiological events that results in abnormalities in the metabolism of both tau and APP/Aβ together with abnormal aggregates of these proteins. A large body of evidence also suggests that synaptic and axonal degeneration with cytoskeletal abnormalities and deficits in axonal transport play an early and important role in AD pathogenesis (Kanaan et al., 2012). Since the initiating event(s) in TBI and CTE are apparent, knowledge from TBI/CTE neurobiology may serve to

improve our understanding of AD and vice versa. In the pathogenesis of AD, it is still under debate whether abnormalities in tau and APP/Aβ metabolism serve a pathogenic role and trigger chronic neurodegeneration, or whether they represent epiphenomena as tissue responses to the neuronal degeneration. While there are certainly important differences between TBI/CTE and AD, given the significant overlap and similarities in pathology, there is still much that can be gained from closely cross-comparing the molecular and cellular mechanisms involved in both of these neuropathological processes.

At present, there is no pharmacological therapy for CTE. However, in contrast to most neurodegenerative disorders, actions can be taken to prevent CTE, particularly in various professions in which traumatic injuries are more likely to occur. For example, in contact sports such as American football, increased awareness of CTE has resulted in action plans by the National Football League to make the sport safer (Ellenbogen et al., 2010). In 2005, the Word Medical Association (WMA) recommended the general ban of boxing because of the basic intent of the sport to inflict bodily harm on the opponent (WMA, 2005). Apart from such a drastic action, there may be alternative ways to make contact sports such as boxing safer, all of which are based on reducing the number of, or impact from, head punches during a bout. A logical option would be to introduce rule changes with fewer rounds in professional boxing, since it is a logical conclusion that the lower incidence of severe acute brain injury and deaths in amateur as compared with professional boxing, as well as the much lower incidence of chronic brain problems in retired boxers, is related to the lower number of rounds in a bout in amateur boxing. Experimental studies suggest that protective equipment may give a reduction of the impact from a punch (Bartsch et al., 2012), but it is noteworthy that boxing headgear is mandatory only in amateur boxing and gloves are also thicker with more padding. Thus, a change in rules to make headgear and gloves with thicker padding also mandatory in professional boxing and martial arts may reduce risk for CTE and is also recommended by the Word Medical Association (WMA, 2005). Lastly, strictly adhering to the recent consensus guidelines for removal of an athlete with concussion from play, recommended by the large international sports organizations (McCrory et al., 2009), in boxing may have a definite impact on both acute concussions and severe brain injury and the prevalence of CTE.

Observations from professional athletes have begun to provide insight into TBI and CTE. As noted above, the development of animal models of head injury is revealing underlying mechanisms, and these approaches may prove to be useful in developing strategies to prevent and treat brain injury. Yet, it is clear that TBI and CTE are significant public health issues and significant efforts are needed to improve prevention, diagnosis, and treatment of these conditions.

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