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Review

Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis

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ABSTRACT

Traumatic brain injury (TBI) represents a significant cause of death and disability in industrialized countries. Of particular importance to patients the chronic effect that TBI has on cognitive function. Therapeutic strategies have been difficult to evaluate because of the complexity of injuries and variety of patient presentations within a TBI population. However, pharmacotherapies targeting dopamine (DA) have consistently shown benefits in attention, behavioral outcome, executive function, and memory. Still it remains unclear what aspect of TBI pathology is targeted by DA therapies and what time-course of treatment is most beneficial for patient outcomes. Fortunately, ongoing research in animal models has begun to elucidate the pathophysiology of DA alterations after TBI. The purpose of this review is to discuss clinical and experimental research examining DAergic therapies after TBI, which will in turn elucidate the importance of DA for cognitive function/dysfunction after TBI as well as highlight the areas that require further study.

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Abbreviations: AC, adenylate cyclase; ADHD, attention deficit hyperactivity disorder; AMH, amantadine hydrochloride; AMPH, amphetamine; BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CCI, controlled cortical impact; CNS, central nervous system; CREB, cAMP responsive element binding; CSF, cerebrospinal fluid; DA, dopamine; DARPP-32, dopamine and cAMP-regulated phosphoprotein mKDa 32; DAT, dopamine transporter; DLPFC, dorsolateral prefrontal cortex; DOPAC, dihydroxyphenylacetic acid; DRS, disability rating scale; ERK, extracellular regulated kinase; FP, fluid percussion; GABA, gamma amino-butyric acid; HD, Huntington's disease; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen activated protein kinase; Mglut-5, metabotropic glutamate receptor-5; MPD, methylphenidate; MWM, Morris water maze; NAcc, nucleus accumbens; NE, norepinephrine; NMDA, N-methyl-D-aspartic acid; NTF, neurotrauma foundation; PD, Parkinson's disease; PET, positron emission tomography; PFC, prefrontal cortex; PKA, protein kinase A; PKC, protein kinase C; PP1, protein phosphatase-1; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B (calcineurin); SPECT, single photon emission computed tomography; SN, substantia nigra; T34, threonine-34; T75, threonine-75; TBI, traumatic brain injury; TH, tyrosine hydroxylase; VTA, ventral tegmental area; WM, working memory.

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1. Introduction

1.1. Traumatic brain injury

Traumatic brain injury (TBI) is the leading cause of death and disability in individuals less than 45 years of age in industrialized countries (Bruns and Hauser, 2003). Each year an estimated 1.4 million Americans experience a TBI and 80,000 to 90,000 suffer long-term substantial loss of function (Rutland-Brown et al., 2006). Clinical studies have shown that 10–15% of individuals with mild TBI have persistent cognitive and behavioral complaints. Outcomes from moderate TBI are much less favorable with some estimates suggesting that 50% of these individuals endure long-term injury-related disabilities (Kraus et al., 2005). This places an enormous economic burden on the U.S. healthcare system with an estimated cost of $9–10 billion in acute care and rehabilitation annually. This cost is in addition to lost earnings, social services, and the cost to family members who must care for TBI survivors. TBI also represents a global healthcare crisis with an estimated 2% of the world's population suffering from chronic symptoms of brain trauma, equating to more than 120 million individuals (NIH, 1998; Ragnarsson, 2002). For these reasons it has been a long sought goal of TBI researchers to understand the mechanisms of chronic disability after TBI to help develop treatment strategies that may assist patients with cognitive recovery.

However, researching chronic disability following TBI has posed a unique challenge to both clinical and experimental researchers. TBI is a highly variable and extremely complex phenomenon. Following the acute primary injury, which often consists of a focal contusion and more diffuse structural damage, there are a series of subsequent secondary responses, which include, but are not limited to, excitotoxicity, ischemia, oxidative stress, and ongoing structural and chemical alterations (Kochanek, 1993; DeKosky et al., 1998; Park et al., 2008). Traditionally, research in recovery of function after TBI has focused on preventing or manipulating early events in order to prevent chronic dysfunction. Drugs inhibiting apoptosis, blocking glutamate-induced excitotoxicity, or attenuating oxidative stress were designed to reduce cell loss with the premise that neuronal sparing would enhance recovery (Faden et al., 1989; Jennings et al., 2008). Unfortunately, the neuroprotective effects observed in the TBI laboratories have not translated successfully to the clinic (Gualtieri, 1988; Tolias and Bullock, 2004). In contrast, therapeutics used during the rehabilitative phase have shown more promise in addressing long-term disability, although they do not necessarily demonstrate the same level of neuroprotection as drugs designed to inhibit apoptosis or block excitotoxicity (Gualtieri, 1988; Rees et al., 2007).

The failure of translating experimental preventative strategies to clinical efficacy has raised the question about what events in TBI are crucial for long-term outcome. The development of clinically relevant small animal models has greatly assisted the understanding of both acute and chronic TBI-induced alterations in brain chemistry. The two most widely used models of TBI are fluid percussion (FP; Dixon et al., 1987) and controlled cortical impact (CCI; Lighthall, 1988; Lighthall et al., 1989; Dixon et al., 1991; Kline et al., 2001; Kline and Dixon, 2001). Both models produce clinically relevant brain pathology as well as behavioral and cognitive dysfunction in rats and mice (Dixon et al., 1987, 1991; Hamm et al., 1992, 1996a,b; Fox et al., 1998, 1999; Kline et al., 2002, 2007a,b; Wagner et al., 2002, 2004; Cheng et al., 2007, 2008; Hoffman et al., 2008a,b). Animal studies (Bramlett and Dietrich, 2002; Lifshitz et al., 2007) and human positron emission tomography (PET) imaging (Langfitt et al., 1986; Fontaine et al., 1999; Donnemiller et al., 2000) have shown that in addition to overt damage (e.g., cortical lesions and hippocampal cell loss), there exist areas of chronic dysfunction previously unappreciated, particularly in the striatum and thalamus, which are regions known to have important roles in cognitive, motor, and emotional processing (Vertes, 2006).

The aims of this review are to: (1) highlight the role of dopamine (DA) in cognition and its functional anatomy relevant to TBI; (2) outline clinical research that has demonstrated potential efficacy of DAergic medications in the treatment of TBI; (3) provide an overview of observed changes in DA signaling and anatomy in experimental models, and outline the importance that these alterations have on cognitive and behavioral deficits; and (4) assess future areas of DA systems research in TBI. This review is not meant to be an exhaustive discussion of DA and cognition, but rather is intended to highlight the role(s) DA plays in persistent cognitive dysfunction after TBI, which may provide insight into potential mechanisms and therapeutic targets for chronic cognitive dysfunction. For recent reviews on DA cellular function and DAergic mediated cognition, see Verheij and Cools (2008) and El-Ghundi et al. (2007), respectively.