Behavioural Brain Research 267 (2014) 156–172

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Remote effects on the striatal dopamine system after fluid percussion injury

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HIGHLIGHTS

- Tonic and bursting dopamine release, reuptake and release probability were suppressed on both sides of striatum in 6-Pa injured animals.
- The parameters were affected at the subacute stage on both sides of striatum in 2-Pa injured animals.
- The turnover rate of dopamine was not affected in 2-Pa injured animals.
- The increasing microglia amount was found on both sides of striatum at 1 day, 1 week, and 8 weeks after injury.

ARTICLE INFO

Article history:
Received 12 December 2013
Received in revised form 14 March 2014
Accepted 18 March 2014
Available online 25 March 2014

Keywords:
Fluid percussion injury
Dopamine releasing and reuptake
Fast-Scan Cyclic Voltammetry (FSCV)
High-pressure liquid chromatography (HPLC)
Neuroinflammation

ABSTRACT

Purpose: To investigate the effects of traumatic brain injury (TBI) on the dopamine system in the brain at different distances from the impaction site, we compared the release, reuptake, metabolism, and release probability of dopamine on the sides of the brain ipsilateral and contralateral to the injury at different time points after varying severities of fluid percussion injuries.
Materials and methods: Tonic (1-pulse evoked) and bursting (10-pulse evoked) dopamine release changes in the ipsilateral and contralateral sides of the striatum resulting from mild (2-Pa) and severe (6-Pa) levels of fluid percussion injury were analyzed at the acute (2 h and 24 h), subacute (1 and 2 weeks), and chronic stages (4, 6, and 8 weeks) after injury by using fast scan cyclic voltammetry to measure brain slices. The metabolic rate of striatal dopamine was surveyed using high-performance liquid chromatography. The microglia reaction was analyzed using immunohistochemistry at each stage.
Results: In 6-Pa injured animals, for both tonic and bursting dopamine release, reuptake and release probability were suppressed on both the ipsilateral and contralateral sides of the striatum from the acute to the chronic stage. These neuronal activities were also affected at the subacute stage on both sides of the striatum in 2-Pa injured animals. The turnover rate of dopamine was not affected in the 2-Pa injured animals but increased gradually during the chronic stage in the 6-Pa injured group.
Conclusion: TBI suppresses dopamine release and reuptake and affects the metabolic rate and release probability of dopamine on the sides of the nigrostriatal system both ipsilateral and contralateral to the injury during both the acute and subacute stages after the injury.

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http://dx.doi.org/10.1016/j.bbr.2014.03.033
0166-4328/

1. Introduction

Traumatic brain injuries (TBIs) consist of a wide range of injuries, from the minor and inconsequential to the severe and disabling [1]. The sequelae of a TBI can vary and depend on the degree of the injury and the structure involved [2]. Among these sequelae are neurobehavioral changes, such as difficulties with attention, planning, problem solving, and memory, which are collectively referred to as frontal lobe syndrome, the hallmark neuropsychiatric response to TBI in humans [3].

In a severe traumatic brain injury including parenchymal destruction and cerebral hypoperfusion resulting from primary or secondary insults of a TBI [4], transient or permanent neuropsychological deficits are induced, including time dysperception [5]; post traumatic stress disorder (PTSD) [6]; attention, learning and memory problems; and disruption of higher-order executive functions [7]. All of these changes are thought to be related to dopamine system impairment [8,9]. In addition, dopamine level changes relating to CSF alterations in severe TBI patients have also been found [10].

In cases of mild TBI, no gross tissue damage occurs at the time of trauma. However, clinical neurological consequences of trauma develop over time and, for the most part (in approximately 85% of cases), regress within a few months after injury [2]. These "lesionless" injuries often result in deficits in reaction times and spatial memory function, as well as an increased occurrence of headaches, dizziness, sleep disturbances, and other emotional and behavioral changes [3,4]. Although the mechanisms of these deficits are poorly understood, there is extensive evidence that dopaminergic lesions of the frontal cortex, innervated by mesocortical dopamine (DA) projections, can lead to persistent cognitive and behavioral deficits [11,12].

There is much data from basic research [13–16] and clinical studies [12,17,18] showing that dopaminergic systems are altered after TBI; evidence has also indicated that these changes may respond to pharmacological intervention with dopaminergic receptor agonists [11,12,19] and that restoration of DA neurotransmission is beneficial after TBI [15,20,21]. Clinical studies using DAergic agonists traditionally have examined DA enhancement therapies in the chronic or recovery phases after TBI. Methylphenidate (MPD), a DA transporter inhibitor, has been shown to benefit memory and attention in TBI patients when administered chronically [22]. The administration of amantadine hydrochloride (AMH) [23,24] and bromocriptine [12] during the recovery phase has also produced improvement in arousal and cognitive outcomes in TBI patients. In the intensive care unit, dopamine agonists (DA) have been used in traumatic brain injury (TBI) patients to augment or accelerate cognitive recovery and rehabilitation. PubMed reviews reveal that methylphenidate, amantadine, and bromocriptine are used clinically [25].

Therefore, a TBI will not only induce focal damage to brain parenchyma but also global effects that affect the dopamine system, including effects on the central nervous system contralateral to the site of the injury. To date, the contralateral side of the injured brain and clarification of the relationship between cognitive deficits and remote site injuries have been documented [14,16,20]. However, the dynamics of dopamine release on the side of the brain contralateral to the injury are still unclear. So understanding the remote injuries caused by TBI is crucial for determining the mechanisms of TBI-induced sequelae and for developing clinical therapeutic strategies. To address this issue, we have, in the present study, analyzed dopamine release, metabolism and releasing probability by using fast scan cyclic voltammetry (FSCV) and HPLC, in addition to comparing the effects of TBI on the ipsilateral and contralateral striatal dopamine system, with the contralateral hemisphere defined as "remote."

2. Materials and methods

2.1. Animals

Young adult, male Sprague–Dawley rats (BioLASCO Taiwan Co., Ltd., ROC) were used in accordance with the regulations of the National Defense Medical Center (NDMC) Animal Care and Use Committee. Animals either received a fluid percussion injury ($n = 44$) or were sham controls ($n = 21$). Animals were provided with food and water ad libitum and housed in a 12-h light-dark cycle.

2.2. Fluid percussion traumatic brain injury

A fluid percussion device (model HPD-1700, Dragonfly R&D, USA) was used to produce TBIs in rats, as described by Matsushita et al. [10,26]. Briefly, with this device, a fluid pressure pulse was generated in a 17.5 mm bore stainless steel cylinder with a 76.2 mm piston stroke, and the device was connected to cranial Luer adapters using a flexible high-pressure tube with an inner diameter of 2.3 mm. The entire device system was filled with sterile water. Injury was induced by striking the piston with a weighted metal pendulum released from predetermined heights. The resulting rapid injection of a small volume of saline into the closed cranial cavity caused a pulse of increased intracranial pressure that, in turn, caused a deformation in the brain. Pressure pulses were measured extracranially with a pressure transducer, recorded on a digital real-time oscilloscope (TDS210, Sony Tektronix Corp., Japan), and then analyzed by WaveStar software (Sony Tektronix Corp., Japan), based on prior instrument calibration, and expressed in atmospheres (atm). The fluid percussion device delivered transient pressure fluid pulses with a constant wave form and duration (17–21 ms) that caused brain injury [11].

2.3. Surgical preparation and fluid percussion model

Six-week-old male SD rats weighing 200–250 g were anesthetized with chlorohydrate (4 mg/100 mg). While the animals were in a stereotaxic frame, the scalp and temporal muscle were reflected. A craniectomy of 4.8 mm in diameter was performed over the right parietal cortex, 3.8 mm posterior to the bregma and 2.5 mm lateral to the midline, taking care not to penetrate the dura [12]. A cranial Luer adapter with an inner diameter of 2.5 mm was placed on the craniectomy site and tightly mounted onto the skull using dental acrylic resin.

Animals were housed for 48 h following the surgical procedure and then reanesthetized with ketamine (75 mg/kg) and medetomidine (0.5 mg/kg). The cranial Luer adapter was filled with saline and attached to the fluid percussion device. Animals were subjected to sham (control, $n = 21$), low (1.9 ± 0.2 atm, $n = 22$), or high (6.0 ± 0.5 atm, $n = 22$) fluid percussions. Each value of fluid percussion corresponded to the theoretical amount of potential material energy calculated using a trigonometric function table. All animals subjected to low or moderate fluid percussions survived during the experimental period, whereas 50% of the animals subjected to high fluid percussions became immediately apneic and never recovered. Survival rates were closely consistent with those reported by Matsushita et al. (2000) and McIntosh et al. (1989) [26,27]. Procedures using animals were approved by the ethical committee on animal experiments at the NDMC.

2.4. Brain slice preparation for FSCV recording

The brain slices were prepared according to a protocol that has previously been described [28,29]. Animals were decapitated using a guillotine, and their brains were removed and transferred to a beaker containing the following oxygenated ($95\%O_2/5\%CO_2$),