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*Neuroscience*

# Inositols and Traumatic Brain Injury Biomarkers – Time Dependent Studies

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(Presented by Academy Member David Mikeladze)

**Abstract.** Traumatic brain injury (TBI) represents a spectrum of brain injuries, which remains an unsolved health problem globally. TBI is often followed by a number of severe and long-lasting complications, which are accompanied by changes in expression of some compensatory or damage-related biochemical markers, such as SOD1, PSD95 and GFAP. We have previously shown that Myo-inositol has a long-term effects on TBI-induced transcriptomic and epigenetic changes. However, nothing is known about early effects of Myo-inositol or other biologically active inositols as Scyllo-inositol and D-chiro-inositol on TBI-induced biochemical changes. Using controlled cortical injury model of TBI we aimed to evaluate the effects of inositol isomers on the expression of the important biochemical markers of TBI. The expression of biochemical markers was studied in neocortical and hippocampal samples on the 7th and 14th days after TBI by SDS gel electrophoresis, Western immunoblotting approach. Our results indicate the time-dependent and region-specific changes of potential biomarker protein molecules after TBI. Some of these changes could be reversed by inositol treatment in a way that could weaken the TBI induced pathological molecular changes. © *2025 Bull. Georg. Natl. Acad. Sci.*

**Keywords:** traumatic brain injury, inositols, SOD1, PSD95, GFAP

## Introduction

Traumatic brain injury (TBI) occupies one of the key positions among neurological problems since it may affect any individual, at any age with various severities and diverse consequences. Due to its complex nature, TBI and its associated problems remain a challenge for the modern neuroscience [1]. The impact of TBI can affect multiple areas and trigger alterations at various levels of the brain activity, frequently leading to the long-term disabilities. Because of such a complex nature, TBI is still a challenging medical and scientific issue. The best TBI treatment strategy would strongly inhibit basic pathological biochemical and physiological processes occurring shortly after injury and prevent development of devastating outcomes. One of the

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ways to accomplish it is to study the effects of candidate compounds on the biomarkers of TBI.

Our interest was to study the effects of inositol family members on basic biochemical processes connected with the early stages of TBI and thoroughly explore molecular mechanisms of their action. Inositols are cyclic carbohydrates with a six-carbon ring and comprise seven natural (myo-, scyllo-, muco-, D-chiro-, L-chiro-, neo-, and cis-inositol) and two unnatural forms (allo- and epi-inositol) [2]. They show beneficial effects for various pathological conditions [3-6]. Recently, we have shown that myo-inositol (MI) treatment has a significant effect on long-term epigenetic and transcriptomic changes in hippocampus after TBI by modulating immune responses and biological pathways of inflammation [7].

Several basic biochemical and physiological processes are associated with TBI including oxidative stress [7-9], changes in synaptic transmission [10-12] and neuroinflammation. The pathophysiological and biochemical changes occurring after trauma are associated with the generation of biomarkers, importance of which has drawn much attention [13].

In the present study, we aimed to explore the role of MI, scyllo-inositol (SCI) and D-chiro-inositol (DCHI) treatment on the levels of protein molecules which are well established to be involved TBI induced changes. One of the pathways of DCHI action is production of intracellular messenger – pinitol (3-O-methyl ether of DCHI), which is involved in insulin signaling [14]. To further elucidate the mechanisms of DCHI possible effects in our experimental design, we also included metformin (METF) treated group, a compound known to improve insulin sensitivity [15].

We carried our experiments using controlled cortical impact model (CCI) of TBI [16]. The following proteins were studied: superoxide dismutase 1 (SOD1), glial fibrillary acidic protein (GFAP) and postsynaptic density protein 95 (PSD95). These proteins were chosen based on the following reasons: (i) oxygen radicals play important role in the pathophysiological processes of acute traumatic brain injury [17, 18]. Following TBI, excessive oxidative stress overloads the endogenous cellular antioxidant system leading to cell death and SODs form the front line of defense against damage caused by reactive oxygen species (ROS) [19, 20]; (ii) Oxidative stress also has effect on PSD 95 expression, which is the main component of postsynaptic density complex. Post-TBI changes in PSD95-levels are markers of synaptic degeneration [21]. GFAP is also considered as a marker of TBI [13].

## Materials and Methods

Experiments were performed on three main groups of adult male laboratory mice (*Mus Musculus* – 25-30g): (i) intact group (INT); (ii) sham – operated group (SHAM) and (iii) CCI treated group (TBI). Each group included 5 subgroups treated with the following compounds: (a) SAL, (b) MI, (c) SCI, (d) DCHI and (e) METF. Depending on a protein, brain region or time point each subgroup consisted of 5 or 6 mice.

Intact animals included in the first group were injected with compounds of study without any prior surgical intervention. The second group underwent sham operation without TBI, and the third group included experimental animals with traumatic brain injury. TBI was performed using a pneumatic controlled cortical impact device (AMS 201) as described in our previous publication [7].

The concentrations of injected compounds were: MI – 30 mg/kg, SCI – 5 mg/kg, D-CHI – 1 mg/kg, METF – 50 mg/kg. Concentrations of inositols were chosen based on our previous studies showing the best effects on KA induced epilepsy [22]. The first injection of compounds was made 2 hours after the TBI operation, and the next injection was made 5 hours later. In the following days – injections were done in the morning and in the afternoon. On the 7th and 14th days, one hour after the final injection, experimental animals were decapitated and the following brain regions were

excised: ipsilateral and contralateral cortex, ipsilateral and contralateral hippocampus.

SDS gel-electrophoresis and Western immunoblotting were performed as described previously [22]. Standard immunochemical procedures were performed using primary antibodies against proteins of our interest: (i) recombinant anti-SOD1 (Abcam ab51254); (ii) anti-PSD95 antibody (Abcam, ab12093) (iii) recombinant anti-GFAP antibody (Abcam ab68428), and corresponding secondary antibodies. LabWorks 4.0 (UVP) software was applied for the measurement of optical densities of immunostained bands.

**Statistical analysis.** On the first step the obtained data, a two-way analysis of variance (ANOVA) was performed with the following factors; treatment group (Intact, Sham-operated, TBI), compound (Saline, MI, SCI, DCHI and METF) and their interactions. Contrasts between individual groups for a given brain region and time point were assessed through Tukey's Honestly Significant Difference (HSD) test. All results with P<0.1 are provided.

## Results

**Immunostaining.** Antibodies against PSD95, GFAP and SOD1, reacted with the protein band of 95 Kda, 50 KDa and 17 Kda respectively (Fig. 1A, Fig. 2A). The optical densities of immunostained bands were in a linear correlation with the amount of loaded proteins.

**Postsynaptic density protein (PSD-95). 7 Days – ipsilateral cortex.** The factor "Compound" exerted significant influence on the amount of PSD95 in the ipsilateral cortex ($F_{4,75}=3.18$, $P=0.018$). The interaction between the factors "Treatment Group" and "Compound" is also significant ($F_{8,75}=5.08$, $P=0.0001$). Several significant differences are observed between the groups (Fig. 1B). TBI (TBI + SAL group) induces significant and strong decrease in the amount of PSD95 as compared to INT+SAL group ($P=0.021$) and most importantly MI treatment restores it. PSD95 amount in the TBI+MI group significantly exceeds TBI+SAL group ($P=0.055$), Fig. 1B. From other significant effects it should be noted that sham operation is also associated with significant decrease of PSD95 as com-

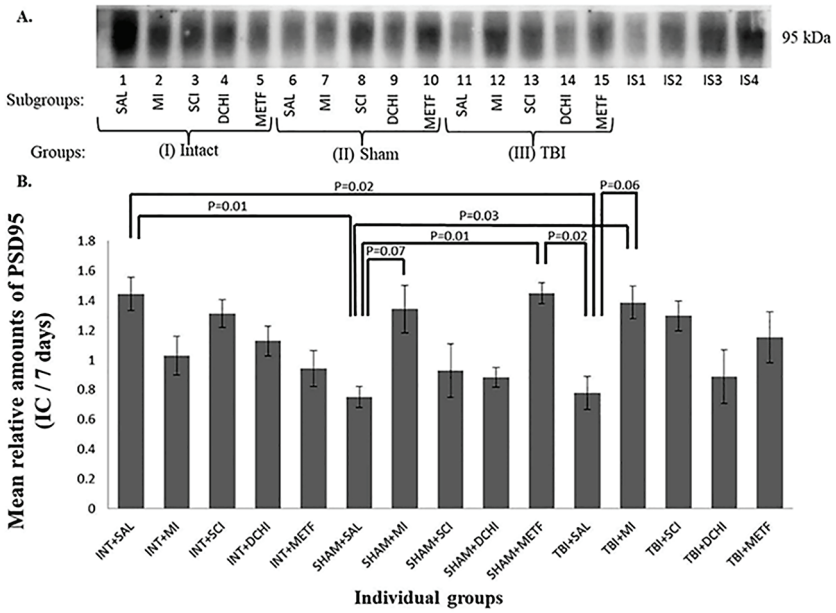


**Fig. 1.** The autoradiograph of PSD95 protein (A) and the mean levels ± sem of PSD95 (B) in the ipsilateral cortex of different groups of mice on 7th day after experiment. Significant differences according to the Tukey multiple comparisons are indicated.

pared to: (i) INT+SAL (P=0.012); (ii) SHAM+ METF (P=0.011) and (iii) SHAM+MI group (P=0.066). The amount of PSD95 in TBI+SCI group is higher as compared to TBI+SAL group.

**7 Days – contralateral cortex.** The effect of the factor "Treatment Group" is significant (F2,75= 4.21). However, no significant differences were detected between the groups.

**7 Days – ipsilateral hippocampus.** In ANOVA there is a weak "Treatment Group" – "Compound" interaction F8,75= 1.89 P=0.073. The amount of PSD 95 is decreased in TBI+SAL group as compared to INT+SAL group (P=0.099).

**7 Days – contralateral hippocampus.** The interaction between the factors "Treatment Group" and "Compound" is significant (F8,75=2.50 P = =0.018). The amount of PSD95 in TBI+SAL group is significantly lower as compared to TBI+SCI group (P=0.009). Thus, SCI treatment counteracts the effect of TBI on PSD95 – one of main components of post-synaptic densities.

**14 Days –** no significant differences are detected between the groups for all studied brain structures and treatment compounds.

**Summary 1.** TBI induces decrease in the amount of PSD95, which depending on the brain region and time after injury, is partially rescued either by MI or SCI.

**Superoxide dismutase 1 (SOD1). 7 Days – ipsilateral cortex.** There is a significant effect of "Compound" in ANOVA (F4,75= 3.30, P = 0.018). Effect of interaction between the two factors is also significant (F8,75= 2.49, P = 0.018). In spite of these effects, weakly significant difference is observed only between TBI+SCI and –Sham+SAL groups; the mean level of SOD1 is higher in TBI+SCI group (P = 0.09).

**7 Days – contralateral cortex.** The effect of the group as well as interaction between the factors "Group" and "Compound" is significant (F2,75= 4.08, P = 0.02 and F8,75= 2,18 P = 0.039 respectively). The mean level of SOD1 in TBI+SCI group

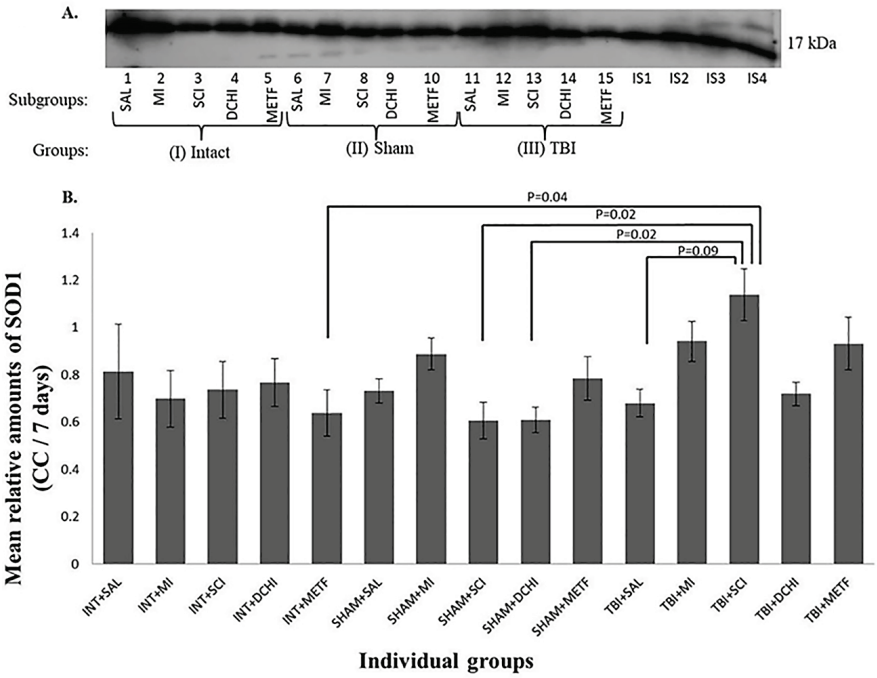


**Fig. 2.** The autoradiograph of SODI protein (A) and the mean levels ± sem of SODI (B) in the contralateral cortex of different groups of mice on 7th day after experiment. Significant differences according to the Tukey multiple comparisons are indicated.

is significantly higher as compared to: (i) SHAM+ SCI (P = 0.02); (ii) SHAM+DCHI (P = 0.022) and (iii) INT+METF (P = 0.042). At last, but not least the mean amount of SOD1 in TBI+SAL is weakly significant less as compared to TBI+SCI (P = 0.093), Fig. 2B.

**7 Days – ipsilateral hippocampus.** No significant effects were detected in two-way ANOVA.

**7 Days – contralateral hippocampus.** The effect of factor "Group" was minimally significant (F2,75=0.07). The mean amount of the protein in sham-operated group is lower as compared to intact group (P = 0.06).

**14 Days –** no significant differences are detected between the groups for all studied brain structures and treatment compounds.

**Summary 2.** TBI induces the decrease in the level of SOD1 and SCI treatment for 7 days after treatment undoubtedly helps to keep SOD1 on a control level.

**Glial fibrillary acidic protein (GFAP). 7 Days – ipsilateral and contralateral cortex.** No significant effects were detected in ANOVA.

**7 Days – ipsilateral and contralateral hippocampus**. ANOVA did not reveal any significant results.

**14 Days – ipsilateral, contralateral cortex and ipsilateral hippocampus.** No significant effects of any treatment were revealed in ANOVA analysis.

**14 Days – contralateral hippocampus**. The effect of compound was significant (F4,60 = 2.52, P = 0.05, Supplementary Table S5.3). The level of GFAP is significantly lower in SCI treated mice as compared to MI treated ones (P = 0.007). In general SCI treatment decreases the GFAP level.

**Summary 3.** The TBI does not have any clear effect on GFAP amounts in the studied brain regions and hence no effects of studied compounds were evident.

## Discussion

The obtained results demonstrate that: (i) TBI and partially SHAM operation have significant effects on studied protein levels; (ii) variety of effects depends on a studied protein, time after TBI, brain region and side and (iii) inositol isomers have different effects on these changes.

Neuropathological conditions generally are associated with molecular changes which are different by their nature. These changes: (i) could contribute causally to the pathological conditions, though parts of them are compensatory and (ii) could be non-contributory. The nature of some of these changes could be changed over the time; initially they could be beneficial against pathological consequences, but subsequently contribute to them. We will try to discuss our obtained data and other available information within this view.

**PSD95**. PSD95 belongs to the group PDZ scaffold proteins and is involved in trafficking, anchoring and clustering of glutamate receptors. PSD95 is also a key component in organization of large signaling complexes and regulates the dynamics of cytoskeletal structures [23]. Our data indicate that PSD95 level drops down drastically in the ipsilateral cortex on 7$^{th}$ day of experiment and MI treatment restores it. The level of this protein is also higher in TBI+SCI group as compared to TBI+SAL group. In our previous study, we have shown that the number of neuronal cells in CA1 and CA3 subfields of hippocampus is decreased after KA induced status epilepticus and MI posttreatment halts this reduction [24]. We suggest that MI in this case also is involved in neuroprotection.

**SOD1**. SODs are a group of ubiquitously expressed enzymes which organize a major defense line against reactive oxygen species (ROS)-mediated injury [9]. Neurodegenerative conditions are accompanied with a decreased activity of SOD1 [9, 25]. Our experiments revealed that SOD1 expression on 7$^{th}$ day of experiment in the contralateral cortex of TBI+SCI group is higher as compared to TBI+SAL group. Such a pattern improves defense system of the brain against oxidative stress. On 14$^{th}$ day of experiment there is a weak decrease in the

amount of enzyme in the ipsilateral cortex and hippocampus and inositols do not have any significant effect on it. Thus, favorable effect is achieved by SCI.

**Inositol isomers and mode of their action**. Our previous research has shown that inositols have common as well as isomer-specific protein targets of action [22]. Specific enzymes – epimerases are converting MI to SCI or MI to DCHI [26]. The existence of such enzymes indicates for the physiologically important and at the same time, for specific roles of SCI and DCHI. Our present study also reveals differential effects of inositol isomers – the most clear effects are observed for SCI, then for MI and practically no effects for DCHI.

For MI, we formulated three possible modes of action in the weakening of epileptogenesis process: (i) normalization of cellular stress by its osmolyte properties; (2) modulation of phospoinositide signalling pathways and (iii) modulation of gamma-aminobutyric acid A receptors [22]. Which of them, or any other possible mode of action are involved in their effects in TBI, is a matter of further studies.

## Conclusion

Our results indicate the time-dependent and region-specific changes of potential biomarker protein molecules after TBI. Some of these changes could be reversed by inositol treatment in a way that could weaken the TBI induced pathological molecular changes.

**Declarations**

**Ethics approval and consent to participate.** All experimental procedures were conducted in accordance with the European Communities Council Directive Guidelines for the care and use of Laboratory animals (2010/63/EU—European Commission) and approved by the animal care and use committee at the Iv. Beritashvili Center of Experimental Biomedicine.

*ნეირომეცნიერება*

# ინოზიტოლები და თავის ტვინის ტრავმული დაზიანების ბიომარკერები – დროზე დამოკიდებული კვლევა

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(წარმოდგენილია აკადემიის წევრის დ. მიქელაძის მიერ)

თავის ტვინის ტრავმული დაზიანება (თტტდ) წარმოადგენს თავის ტვინის დაზიანებების სპექტრს, რომელიც რჩება ჯანმრთელობის გადაუჭრელ გლობალურ პრობლემად. თტტდ-ს ხშირად მოჰყვება პოსტტრავმული ეპილეფსია და სხვა მძიმე, ხანგრძლივი გართულებები, რომლებსაც თან ახლავს ზოგიერთი კომპენსატორული ან დაზიანებასთან დაკავშირებული ბიოქიმიური მარკერის ცვლილება, როგორიცაა სუპეროქსიდ დისმუტაზა (SOD1), პოსტსინაფსური სიმკვრივის ცილა 95 (PSD95) და გლიური ფიბრილარული მჟავე ცილა (GFAP). წინა კვლევაში ნაჩვენები გვაქვს, რომ მიო-ინოზიტოლს აქვს გრძელვადიანი ეფექტი თტტდ-ინდუცირებულ ტრანსკრიპტომულ და ეპიგენეტიკურ ცვლილებებზე. თუმცა, არაფერია ცნობილი მიო-ინოზიტოლის ან სხვა ბიოლოგიურად აქტიური ინოზიტოლების, მათ შორის, სქილო-ინოზიტოლის და D-ქირო-ინოზიტოლის გავლენის შესახებ თტტდ-ინდუცირებულ ადრეულ ბიოქიმიურ ცვლილებებზე. თტტდ-ის კონტროლირებადი კორტიკალური დაზიანების მოდელის გამოყენებით ჩვენ მიზნად დავისახეთ შეგვეფასებინა ინოზიტოლის იზომერების ეფექტი თტტდ-ის მნიშვნელოვანი ბიოქიმიური მარკერების ექსპრესიაზე. ბიოქიმიური მარკერების ექსპრესია შესწავლილი იყო ნეოკორტიკალურ და ჰიპოკამპალურ ნიმუშებში თტტდ-დან მე-7 და მე-14 დღეს SDS გელ- ელექტროფორეზის და ვესტერნ იმუნობლოტინგის მეთოდების გამოყენებით. ჩვენი შედეგები ავლენს პოტენციური ბიომარკერი ცილოვანი მოლეკულების დროზე დამოკიდებულ და უბან-სპეციფიკურ ცვლილებებს თტტდ-ის შემდგომ. ზოგიერთი ინოზიტოლით დამუშავებამ შეიძლება ისე შეცვალოს ბიომარკერების ექსპრესია, რომ შეასუსტოს თტტდ-ით გამოწვეული პათოლოგიური მოლეკულური ცვლილებები.

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