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Changes in Gene Expression of P75 and Trk Receptors in Deprenyl-Treated Spinal Cord Injury Rats

[1]Marjan Heshmati and [2]Alireza Azizzadeh Delshad

[1]Department of Anatomical Sciences and Pathology, Faculty of Medicine, Shahed University
[2]Department of Anatomical Sciences and Pathology, Faculty of Medicine, Shahed University, Opposite Holy Shrine of Imam Khomeini, Khalij Fars Expressway, Tehran, Iran

Abstract: Apoptotic cell death a prominent component of secondary events of spinal cord injury (SCI), may be influenced by neurotrophin receptors p75 and Trks which have been claimed both pro-survival and pro-apoptotic. In the present study to investigate the effects of the putative neuroprotectant, deprenyl, on the expression of neurotrophin receptors in SCI model, adult deprenyl treated rats were subjected to compressive SCI. After 2-72h the spinal cord tissues were processed to detect the p75NTR, TrkA and TrkB mRNA expression through semiquantitative RT-PCR. In the intact samples no expression of p75NTR occurred, whereas SCI induced a series of fluctuant changes and deprenyl put off its expression to 8h. In the SCI-groups the expression of TrkB receptor, changed in a contradictory manner and deprenyl caused an augmented overexpression of TrkB at 2h which tended to decrease in the following time points progressively. The expression of TrkA gene indicated no significant changes up to 4h following SCI, but thereafter its expression increased significantly and deprenyl treatment didn't induce any changes. It can be concluded that deprenyl can exert its neuroprotective effect through inhibiting the expression of p75NTR and upregulating the TrkB receptor in the early first hours following the injury.

Key words: Spinal Cord Injury · Deprenyl · P75NTR · Trk Receptors · Neuroprotection

INTRODUCTION

Spinal Cord Injury (SCI) is a medical emergency caused by acute traumas such as motor vehicle accidents or non-traumatic origins as cancer, infection, vertebral injury and spinal cord vascular disease resulting in a direct injury to the cord itself or an indirect damage to the surrounding tissues or blood vessels where immediate treatment can reduce long-term effects. Most human SCI cases do not involve transection of the cord but are rather due to the compression/contusion injuries with significant vascular complications and ischemia. The pathophysiology of SCI involves an initial primary or mechanical insult followed by a series of secondary events including ischemia, ionic fluxes, free radical production and peroxidation which result in further cell death, particularly apoptosis with the morphological features of chromatin condensation, nuclear fragmentation, cytoplasmic shrinkage and apoptotic body formation followed by phagocytosis [1].

Neurotrophins, which are members of growth factor family, act through the receptors p75 and tyrosine kinases (Trk) exerting both pro-survival and pro-apoptotic effects on neural cells. Despite the identified mechanisms of programmed cell death exerted through these receptors, relatively little is known about the exact role of these receptors in initiating post-spinal cord injury apoptotic cell death in SCI pathophysiology. The p75 neurotrophin receptor (p75NTR), which can influence cellular differentiation and apoptosis, interacts with all of the mammalian members of the neurotrophin family [2] NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) with nearly equal affinities [3] but the Trks bind to individual neurotrophins specifically: TrkA to NGF and NT-3 [4], TrkB to BDNF and NT-4 [5] and TrkC to NT-3 [6].

The efficacy of several drugs have been studied in various models of SCI. Results of in vivo and in vitro studies on the monoamine oxidase B inhibitors (MAOB-Is) rasagiline and deprenyl, which have been

Corresponding Author: Marjan Heshmati, Department of Anatomical Sciences and Pathology, Faculty of Medicine, Shahed University, Tehran, Iran.

considered as putative neuroprotective drugs, have indicated that the MAOB-Is can protect neurons through intervention of plausible mechanisms of neural degeneration such as apoptotic and excitotoxic cell death, mitochondrial impairment, oxidative stress, loss of neurotrophic factors and induction of pro-survival and anti-apoptotic factors. The MAOB-I deprenyl, which has a lot of pharmacological activities some of them not related to its MAOB inhibitory potency, can render protection against dopaminergic, cholinergic and noradrenergic neurotoxins with a complex mechanism of action [7]. In the present study, based on the reported neuroprotective effects of deprenyl in various kinds of neural disorders, we investigated the molecular changes of p75 and Trk mRNA in deprenyl treated SCI rats using a semi-quantitative RT-PCR technique.

MATERIALS AND METHODS

Animals: All experimental protocols of this study were approved by the animal care committee of Shahed University in accordance with the policies established in the guide to the care and use of experimental animals prepared by animal care and all efforts were made to minimize the number of animals and their suffering. 62 female Sprague Dawley rats (Razi Institute, Karaj/Iran) weighing 250-300 g (10-12weeks old) were housed in an air-conditioned colony room on a 12/12 light/dark cycle (22-23°C and 30-40% humidity) three to four per cage with standard pelleted diet and tap water ad libitum for at least 10 days before the beginning of the experiment.

Spinal Cord Injury and Experimental Groups: After anesthetizing the animals (ketamine 100mg/kg/ xylazine 5mg/kg, ip) and exposing the spinal cord through laminectomy, an extradural compression was applied at T6 level for 1 minute by means of a bilateral position oriented Kerr Loughed aneurysm clip applicator (Johnson and Johnson/USA) calibrated to deliver 35g closing force. Following suturing the incision Cephazoline and 5-8ml Lactate serum was administered intraperitoneally to replace the bleeding and the animals were maintained at an ambient temperature of 25-27°C. The applied compression on the spinal cord resulted in a moderately severe SCI with initial complete paraplegia followed by a delayed partial recovery of hind limbs. Manual compression of bladder was performed three times daily and all efforts were done to prevent bladder infection and any injury due to the sensory disorders. The sham groups were only subjected to laminectomy without any compression applied on the cord. The animals were randomly divided into four groups (n =15) all administered 1 hour before the sham or SCI surgery with 2.5 mg/kg deprenyl (CIPLA/ India, dissolved in 1ml saline) or equal volume of saline as the vehicle: group1: SCI + deprenyl, group2: SCI + vehicle, group3: Sham surgery + deprenyl and group4: Sham surgery + vehicle. In every group 2, 4, 8, 24 and 72 hours after surgery 3 of the animals were sacrificed and the T6 segment of the spinal cord was transferred in separate tubes to -80°C for detection of p75NTR, TrkB and TrkA mRNA expression through a semi-quantitative RT-PCR technique. The spinal cord of the remaining two animals was used as the intact group and the positive control in the RT-PCR technique.

RT-PCR Technique:

RNA Extraction: To extract the total RNA, 1000µl of RNX plus solution (Cinnagen/Iran) and 200µl of chloroform (Merk/Germany) were added to the homogenized solution of spinal cord and centrifuged for 15min at 12000g and 4°C. After transferring the upper phase into another tube and adding an equal volume of isopropanol (Merk/Germany) for 45min at 4°C to precipitate the RNA, the mixture was centrifuged again for 15min at 12000g and 4°C. The obtained pellet was washed in 75% ethanol, centrifuged for 5min at 7500g and 4°C and finally dissolved in diethylpyrocarbonate-treated water.

RT-PCR Reaction: cDNA synthesis was performed using 1µg RNA, 1µl MMLV reverse transcriptase (GibCoBRL/ Germany), 1µl oligo (dT) (MWG-Biotech.AG/ Germany), 1µl dNTP (Gibco BRL/ Germany), 0.5µl RNasin (Fermentas/ Germany), 1µl MgCl2 (Cinnagen/Iran) priming in a 20µl reaction. Specific primers for p75NTR, TrkB, TrkA and β2 microglobulin (β2m) as an internal control were obtained from NCBI with the following Gen bank accession numbers: p75NTR - X05137, TrkB - M55291, TrkA- M23325 and β2m - Y00441. Using Generunner software (version 3.02; Hastings Software Inc) a couple of primers were ordered according to the sequence of cDNA of studied genes of Sprague Dawley rats. The sequences of the primers used in this study and their specifications are presented in Table 1. The primers were synthesized by MWG- Biotech Company (Ebersberg/ Germany) as highly purified salt-free grade in lyophilized form. All used primers were blasted against the rat genome to ensure that they are not complementary with the other regions of the genome. PCR primers were expected to amplify 652, 386, 342 and 317 bp segments from p75NTR, TrkB, TrkA and β2m cDNA respectively. PCR (Techne/ Cambridge/ UK) was carried out using 1µl dNTP, 5µl of synthesized cDNA,

Table 1: GeneBank accession numbers, forward and revers promer sequences and fragment size of the studied genes,. P75NTR: p75 neurotrophin recptor; Trk-B: tyrosine kinase B; Trk-A: tyrosine kinase A; β2m: Beta-2 microglobin (as an internal control)

Gene	Accessuion no	Forward 5' → 3'	Reverse 5' → 3'	Size (bp)
p75NTR	X05137	CTG CCA GGA CAA ACA GAA CA	TAT CCC CGT TGA GCA GTT TC	652
Trk-B	M55291	AGC ACA TTG TCA AGT TCT ACG G	ACA TGA TGC TCT CTG GAG GC	386
Trk-A	M23325	AAT GCT CGT CAG GAC TTC CAT C	TCT TGA CCA CTA GTC CCT GAC C	342
β2m	Y00441	CCG TGA TCT TTC TGG TGC TT	TTT TGG GCT CCT TCA GAG TG	317

one unit of Taq polymerase (Promega) and 3µl MgCl2 (Promega) for one minute at 94°C. Then by using 2.5µl primer forward and 2.5µl primer reverse, the PCR amplification was carried out for either 30 (p75NTR), 35 (TrkB), 35 (TrkA) and 35 (β2m) cycles, with the following cycling conditions: 94°C for 30s, 55°C for 30s, 72°C for 40s, with a final extension at 72°C for 10min. In each set of PCR by omitting RT enzyme, negative controls were obtained and the tissues of the spinal cord of a one-day old rat and the cerebellum and spinal cord of adult rats were used as positive controls for p75NTR, TrkB and TrkA respectively.

Quantification of the Intensity of PCR Products: Following separating the PCR products on a 1% agarose gel and visualizing them by ethidium bromide (Merk/Germany), the amount of DNA was quantified by measuring the intensity of light emitted from corresponding band under UV light using Total Lab Phoretix Software. The results were expressed as the ratio of the intensity of the three investigated genes bands (p75NTR, TrkB and TrkA) to that of β2m as an internal control. All experiments were repeated three times and the achieved mean and standard deviation were analyzed by Analysis of Variance (ANOVA) and Tukey tests, where $P<0.05$ was assumed as significant.

RESULTS

The results of the RT-PCR technique have been demonstrated as bands on agarose gel and the ratio of the intensity of the bands of each of the three studied genes to the βm2 gene analyzed by the Total Lab Phoretix software has been demonstrated as mean and standard deviation in several histograms (Figures 1-3). In the intact samples of the spinal cord no expression of p75NTR occurred, but SCI upregulated its expression with a periodic fluctuation pattern at different time points following the injury, resulting in lower amounts at 2, 8 and 72h and significantly higher levels at 4 and 24h (Figure 1a, c). Deprenyl treatment of SCI animals prevented the p75NTR expression up to 4h following the injury, but after 8h it began to be expressed increasingly, with no significant difference between 8 and 24h but at 72h a significant increase occurred (Figure1b, d), indicating the maximum effect of deprenyl in the first hours following the administration with a quickly attenuating manner.

In the intact samples of the spinal cord a low expression of TrkB occurred and SCI caused a periodic fluctuation pattern of its expression with higher levels at 2 and 8h and lower amounts at 4, 24 and 72h, which were almost in contrast with the p75NTR expression pattern,

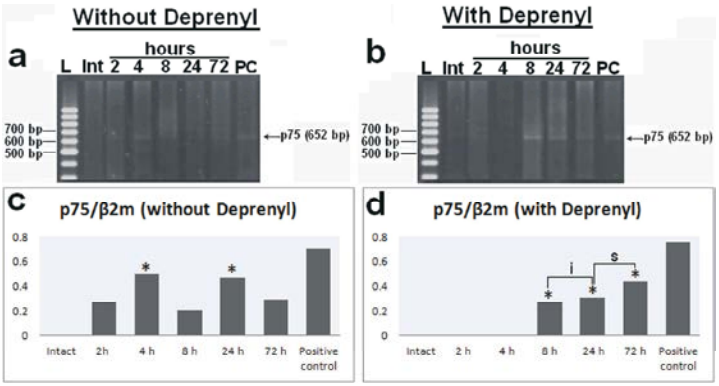

Fig. 1: Expression of p75 following spinal cord injury in rats without (a) and with (b) deprenyl treatment. In rats without any deprenyl treatment at 4 and 24 hours following the SCI the ratio of p75/β2m increased significantly (* = $p<0.05$) but in other time points no significant difference could be seen (c). In animals treated with deprenyl the increase of this ratio was postponed to 8h and thereafter it showed significant differences (* = $p<0.05$) (d). However the difference between the 8 and 24h groups was statistically insignificant (*i*) whereas between 24 and 72h groups a significant difference (*s*) could be seen

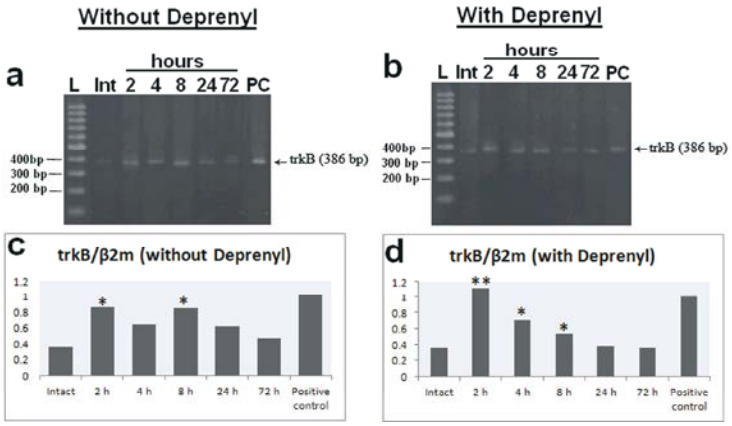

Fig. 2: Expression of trkB following spinal cord injury in rats without (a) and with (b) deprenyl treatment. In rats without any deprenyl treatment at 2 and 8 hours following the SCI the ratio of trkB/β2m increased significantly (* = $p<0.05$) but in other time points no significant difference could be seen(c). In animals treated with deprenyl 2h following the SCI this ratio increased significanyly (**= $p<0.01$) and then tended to decrease progressively, although at 4 and 8h still a significant difference (* = $p<0.05$) could be seen

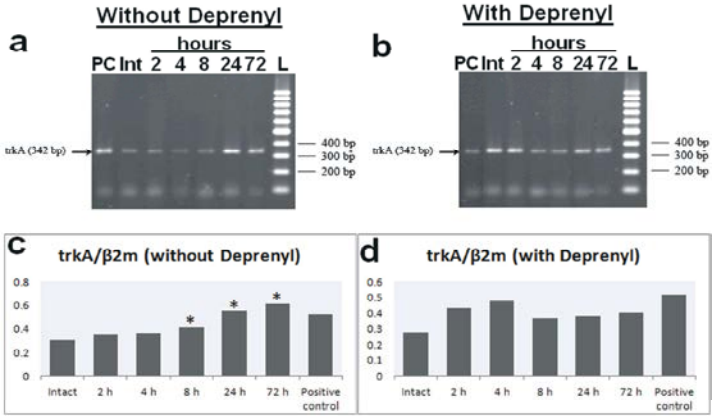

Fig. 3: Expression of trkA following spinal cord injury in rats without (a) and with (b) deprenyl treatment. The ratio of trkA/β2m (c) showed a significant increase in time points longer than 8h (* = $p<0.05$) and in the groups treated with deprenyl no significant difference occurred (d)

except at 72h following the injury where the expression of both genes decreased (Figure 2a, c). Deprenyl treatment of SCI animals resulted in a high expression of TrkB gene at 2h following the injury ($p<0.01$) and progressively diminishing levels up to 72h while still significantly different at 4 and 8h ($p<0.05$) (Figure 2b, d).

In the intact samples of the spinal cord a low expression of TrkA, almost as the same as the TrkB expression, occurred and SCI augmented its expression progressively with significant differences achieved at 8, 24 and 72h ($p<0.05$) (Figure 3a, c). The expression of TrkA in deprenyl treated SCI animals indicated no significant differences with the non deprenyl administered animals (Figure 3b, d). Due to the insignificant variations in the results of the two sham groups their data have not been presented here.

DISCUSSION

Our findings indicated a series of fluctuant changes in expression of p75NTR following the execution of SCI, whereas in intact samples no expression occurred. Investigating the expression of TrkB receptor at the same time points revealed almost contradictory results in comparison to p75NTR. Comparing the expression of TrkA gene with the intact samples indicated no significant changes up to 4h following the SCI but thereafter its expression increased significantly. In the early hours after the SCI the expression of all of the three studied receptors p75NTR, TrkB and TrkA, showed a substantial increase which can be considered as the attempt of the injured cells to survive the initial insult by expressing more receptors for all of the neurotrophic agents, but after 4h

in spite of the continuation of the increase of p75NTR and TrkA, the TrkB expression showed a remarkable reduction. Neurotrophins, although usually taken as pro-survival growth factors, may be involved in the induction of in vivo neuronal death under pathological conditions. Survival/death decisions may depend on a balance between different signaling pathways, so that the presence or absence of a particular receptor signaling may convert a survival to an apoptotic outcome and also it has been estimated that the neurotrophin receptors may have opposite effects on neuronal survival [8].

It has been indicated that p75NTR can exert a constitutive pro-apoptotic effect, but the presence of NGF, perhaps by binding to p75NTR, blocked this effect. P75NTR can in some circumstances play a role in facilitating or transducing the survival effect of NGF. The observed activity of p75NTR depends on the developmental or physiological state of the cell. At least part of the pro-apoptotic effect of p75NTR could be explained by p75-mediated inhibition of TrkA signaling [9]. Endogenous expression of neurotrophins and their Trk receptors in the injured spinal cord is well documented in mammalian CNS [4].

There is a bulk of reports stating that neural injuries such as SCI can bring about changes in expression of p75NTR and Trk receptors which can be involved in the outcome of the injury. Trks are tyrosine kinase receptors that bind selectively to particular neurotrophins and promote the survival of specific populations of neurons during development. P75NTR and Trks, when co-expressed, form a high affinity binding complex that provides specificity in neurotrophin binding and enhances Trk tyrosine kinase signaling and subsequent trophic effects [10].

In the pathogenesis of the SCI, apoptotic cell death as one of the components of the secondary injury following the initial neurotrauma, has been assumed to be involved with the activation of death receptors such as Fas and p75 [11]. Despite the emphasis on the upregulation of p75NTR after SCI [12], it has been reported to have contradictory effects on promoting cell survival or apoptotic cell death. It has been affirmed that neurotrophin binding to p75NTR in the absence of Trk signaling can activate apoptosis in specific cell types [13] and also can affect myelination [14, 15] and neurite outgrowth [16]. These Trk-independent functions of p75NTR have been suggested to be involved in the development of the nervous system and in cellular responses to injury [10]. The intracellular domain of p75NTR can initiate apoptosis through activation of caspases [17-19]. The p75NTR-induced cell death, through releasing cytochrome-c from mitochondria and activation of caspase-9, follows the intrinsic apoptotic death pathway [20]. It has been revealed that the cell death induced by neurotrophin withdrawal which occurs through the intrinsic apoptotic pathway is associated with Bax redistribution from the cytoplasm to the mitochondria, the release of cytochrome c and apoptosis [21]. The p75NTR has also been claimed to be involved in inhibition of axonal regeneration following the SCI [22]. Following a series of in vitro studies on oligodendroglia and neurons, Bamji and his colleagues showed the role of p75NTR on initiating the apoptotic cascade [23] and in another study on the mice suffering partial transection of spinal cord and genetic inactivation of the p75NTR a decrease in oligodendroglial cell death has been reported [24]. Based on some in vitro studies on the roles of p75NTR, its proapoptotic effects seem to be mediated through activation of Jun-N-terminal kinase (JNK) and caspase-9 [20, 25].

On the other hand some studies reported the necessity of p75NTR for improvement of cell survival and locomotor recovery following a compressive SCI [26]. The results of studies on p75NTR suggested a series of complex prosurviaval, proapoptotic [27], or anti-regenerative [16] roles of p75NTR on the outcome of neural insults. There are reports expressing extra roles of p75NTR in addition to initiation of apoptotic cell death so that its inhibition after a SCI may worsen the clinical outcomes [26].

It has been suggested that p75NTR either through enhancing neurotrophin binding with Trk receptors or without any association with these receptors may improve cell survival [26]. Interaction of p75NTR with Trks either increases neurotrophin binding affinity, reduces Trks responses to other ligands or facilitates apoptosis [27]. Ferrer *et al*., (1998) after studying a model of global transient cerebral ischemia suggested the role of an imbalance of p75NTR and TrkB receptor-mediated signals in ischemic brain injury pathogenesis [28]. Therefore, it seems that restoration of the correct ratio of expression of the two receptors can be a candidate target for neuroprotection [29]. Many studies reported that p75NTR in the presence of TrkA enhances the survival signals of NGF while in the absence of TrkA it can activate apoptotic signals [30], whereas some other reports suggested that the signals controlling the p75NTR expression is dissociated from that of the Trks [31]. Beattie and his colleagues (2002) in a study on compressive SCI, concluded the key role of p75NTR activated by pro-NGF, in the initiation of apoptosis of oligodendrocytes after the injury [24]. Since other

members of the TNF receptor family, too, have been indicated to elicit both pro-death and pro-survival signals, the opposing pathways initiated by p75NTR are not entirely astonishing [10]. The consideration that p75NTR ligand is a survival factor and that receptors close to p75NTR were pro-apoptotic proteins led to a hypothesis that p75NTR could be a sort of anti-death receptor that would kill neurons upon NGF withdrawal rather than upon ligand binding. Data declaring that p75NTR when unoccupied by NGF can induce apoptosis, whereas after binding with NGF blocks apoptosis [32], supported the view that an unbound receptor could trigger apoptosis and was the premise of the dependence receptor paradigm [33]. It has also been proposed that p75NTR together with TrkA mediates the survival of neurons during the establishment of target innervations while it induces apoptosis in the early postnatal period [34]. Based on the highly controversial effects attributed to the p75NTR, it appears to act as a modifier protein enhancing or attenuating the cell death depending on the type of the injury, the type of the cell affected and the location of the injury [26].

Our findings indicated that deprenyl could delay the expression of p75NTR in the SCI animals up to 8h following the injury and thereafter it was expressed increasingly, whereas the effect of deprenyl on the Trk receptors caused a high upregulation of TrkB beginning at 2h and decreasing in the following time points and no significant differences of TrkA could be shown. It has been indicated that the MAOB-Is can protect neurons through intervention of intrinsic mitochondrial apoptotic cascade and the induction of pro-survival antiapoptotic Bcl-2 and neurotrophic factors [35]. Deprenyl as a well-known MAOB-I with a wide range of pharmacological activities some of them not related to its MAOB inhibitory potency can render neroprotection probably by reducing neuronal apoptosis [36]. It is known that deprenyl increases BDNF in the cerebrospinal fluid of patients with Parkinson's disease and nonhuman primates [35], increases the ciliary neurotropic factor gene expression in vitro [37], enhances the expression of NT-3 and TrkC receptor mRNA [38] and in concentrations lower than needed to inhibit MAOB, can decrease the oxidative damage [39], through enhancing the synthesis and activity of SOD1, SOD2 and catalase in experimental animals [40]. Since the effectiveness of low concentrations of deprenyl, it has been suggested that not the parent compound itself, but some of its metabolites can be responsible for the anti-apoptotic activity [36]. Ravikumar *et al*., (1998) reported that spinal cord ischemia induces a motor neuron degeneration and locomotor impairment, which can be attenuated by deprenyl treatment given postischemically for 14 days [38].

CONCLUSION

As stated above in the first hours following the SCI the expression of p75NTR increased and of the TrkB decreased considerably which could lead to a prominent apoptotic cell death as a main constituent of secondary SCI sequence. Deprenyl through inhibiting the expression of p75NTR and upregulating the TrkB receptor can provide a putative therapeutic window in the early first hours following the injury, which can be a golden time in preventing the subsequent apoptotic cell death.

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