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Effects of Aspirin and Celecoxib on Rigidity in a Rat Model of Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a degenerative neurodopaminergic disease in nigrostriatum pathway of human and is responsible for most of the movement disorders. Increasing evidence suggests that an inflammatory reaction accompanies the pathological processes caused by Cyclooxygenase (COX) seen in many neurodegenerative disorders, including PD and according to the recent researches chronic use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) decreases the risk of PD in human. In the study the rat left Substantia Nigra Pars Compacta (SNc) have been destroyed using electrical lesion (1 mA; DC; 8 Sec) to induce PD model. Then aspirin (30, 60 mg kg^{-1}) and celecoxib (4, 8 mg kg^{-1}) have been administrated orally to parkinsonian rats. When the animals were suffered to PD Murprogo's Method evaluated the rigidity of parkinsonian rats. Both selective COX-2 inhibitor (celecoxib) and non-selective COX-2 inhibitor (aspirin) decreased the rigidity of parkinsonian rats $p<0.05$ but rigidity recovery after administration the selective COX-2 inhibitor was more than non-selective COX-2 inhibitor. These findings are additional pharmacological information which has suggested the use of NSAIDs as alternative way to treat the rigidity of PD.

Key words: Aspirin, Celecoxib, electrical lesion, Parkinson's disease, inflammation, NSAIDs

INTRODUCTION

COX is the first enzyme in the prostaglandin/ prostacyclin/thromboxane pathway.

It converts arachidonic acid to prostaglandins and thromboxanes, which are collectively known as its metabolites (Smith *et al*., 1991). Three COX isoforms, COX-1, COX-2 and COX-3 have been identified; COX isoenzymes catalyze both the biooxygenation of arachidonic acid to form prostaglandin G_2 to form prostaglandin H_2 in the biosynthesis of prostanoid (Xie *et al*., 1991; Shaftel *et al*., 2003).

COX-1 is the constitutive form of COX and performs a housekeeping function to synthesize prostaglandins, which are involved regulating normal cellular activities (Herschman, 1996). In contrast, COX-2 is the inducible form of COX, as its expression can be induced by inflammatory stimuli or mutagens, tumor necrosis factor alpha (TNF-α) and the transcription factor CCAAT enhancer binding protein (c/EBP) beta. The brain possesses both COX-1 and COX-2 isoforms, also COX-2 up regulation during the stressful conditions such as cerebral ischemia and up regulated by neuronal apoptosis and neurobehavioral defect (Dubois *et al*., 1998; Li *et al*., 2003).

COX-2 appears to be expressed in dendrites and cell bodies of neurons in several areas of the brain such as nigrostriatal pathway, CA-1 hippocampus, amygdala nucleus (Yamagata *et al*., 1993).

COX-2 corresponds to inflammatory and degenerative brain disease (Minghetti, 2004). PD is a degenerative neurodopaminergic disease in nigrostriatum pathway of human and the resultant loss of nerve terminals accompanied by dopamine deficiency in this pathway are responsible for most of the movement disorders (McGeer and McGeer, 2002; Fahn and Przedborski, 2000). Increasing evidence suggests that an inflammatory reaction accompanies the pathological processes seen in many neurodegenerative disorders, including PD (McGeer and McGeer, 2002; McGeer *et al*., 2003). Glial activation is part of a defense mechanism to remove debris and pathogens and promote tissue repair. However, inflammatory activation of microglial cells may contribute to the neurodegenerative process through

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structural invasion and the release of pro-inflammatory cytokines, ROS, NO and excitatory amino acids at synapses and cell bodies (Teismann and Ferger, 2001; Bal-Price and Brown, 2001). In cell culture and animal models, inflammation contributes to neuronal damage and NSAIDs have been shown to provide some neuroprotection in different paradigms (Wu *et al*., 2002) including PD models (Hirsch *et al*., 1998). Reactive microglia inhibits neuronal cell respiration via NO and cause neuronal cell death *in vitro* and *in vivo* (Banati *et al*., 1999; Gao *et al*., 2002). Today investigators have found an uncertain relationship between the use of NSAIDs and PD. They suggest that chronic use of NSAIDs decreases the risk of PD (Asanuma *et al*., 2003). Some studies suggest the role of COX-2 in degenerative diseases such as PD (Teismann and Ferger, 2001).

Until the time of research we have not found any clear evidence that has noticed the use of NSAIDs to treat the rigidity of PD. So in present study we have investigated effect of selective COX-2 inhibitor celecoxib in comparison with non-selective COX-2 inhibitor aspirin on the rigidity of PD.

MATERIALS AND METHODS

Animals: Ninety male albino Wistar rats (200-250 g) were the subjects of the present study. The animals were purchased from Pasteur Institute of Iran and housed in groups of ten in stainless steel cages, handled daily and provided with food and water *ad libitum*. A 12 h light/12 h dark cycle was maintained and the animals were tested during the light cycle. These animal experiments were carried out in accordance with the recommendations from the declaration of Helsinki and the internationally accepted principles in the use of experimental animals.

In this study, we divided animals into 9 groups 10 (Table 1).

In addition, each group contained 10 rats (10 animals/ group).

Drugs and solvents: Aspirin and celecoxib were purchased from Razak and Abidi laboratories (Pharmaceutical Companies, Iran), ketamine and Xylazin from Merck (Germany). Aspirin dissolved freely in glycerin and celecoxib dissolved in Dimethyl Sulfoxide (DMSO) and glycerin and ketamine and Xylazin dissolved in distilled water.

Surgery: Each rat was anesthetized separately by injection of 75 mg kg^{-1} ketamine combined with 8 mg kg^{-1} Xylazin intraperitoneally. Then we prepared the rats for surgery and placed them in the stereotaxic instrument. The left SNc region of the nigrostriatum was targeted. Stereotaxic coordinators for the left SNc region were set at 4.8 mm posterior and -1.6 mm lateral to bregma and 8.2 mm ventral to the surface of the skull according to the atlas (Paxinos and Watson, 1997) and the left SNc was destroyed by lesion maker (1 mili A, Direct Current and 8 sec). Laterally lesion of SNc in each rat caused PD. Then the rats were kept in individual cages for recovery for 7-10 days after the surgery. Estimation of violence and duration of lesion was accepted empirically *in vitro* by determination of clot-dimensions in electrocardiograph gel caused by electrical maker and finally with animal examination and histological studies (Illustration 1) optimal lesion conditions were yielded. The Fig. 1 (A-D) shows the accuracy and the precision of the lesion.

Place and date of the research: This research at the first was done in the Ahwaz Physiology Research Center laboratory of Ahwaz Jondishapour University of Medical Sciences, Iran during the Jun 2006 until Sept 2006. In addition, for further confidence about our previous results the research was well repeated with some modifications with regard to the first research, in the second place [Medicinal Chemistry Department laboratory of Tehran University of Medical Sciences, Iran] during the Jan 2007 until April 2007.

Rigidity evaluation: Murprogo's Method (Murprogo, 1962) in this study, was used to measure the rigidity of animals after orally administration of drugs or vehicles at the times: 0, 20, 40, 60, 90, 120, 180 and 240 min. The

Table 1: Mean of rigidity grades with SEM in investigated groups (N = 10) (Mean±SEM)

	Time (min)							
Group	0	20	40	60	90	120	180	240
Positive control [a]lesion of SNc	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0
Negative control b	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0
Sham	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0	0.0±0
Lesion of SNc + [b]vehicle of aspirin	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0
Lesion of SNc + [c]vehicle of celecoxib	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0	3.5±0
Lesion of SNc + aspirin 30 mg kg^{-1}	3.5±0	3.5±0	3.1±153	2.5±0.133	3.1±0.163	3.5±0	3.5±0	3.5±0
Lesion of SNc + aspirin 60 mg kg^{-1}	3.5±0	2.8±0.163	1.1±0.2	2.1±0.200	2.1±0.164	3.2±0.163	3.5±0	3.5±0
Lesion of SNc + celecoxib 4 mg kg^{-1}	3.5±0	2.7±0.153	2.0±0.2	1.4±0.760	2.2±0.163	2.8±0.163	3.5±0	3.5±0
Lesion of SNc + celecoxib 8 mg kg^{-1}	3.5±0	2.7±0.133	1.6±0.1	1.2±0.076	1.5±0.129	1.9±0.167	2.7±0.213	3.2±0.133

[a]: Substana nigra pars compacta; [b]: Glycrin; [c]: Dimethy isoxide (DMSO) + glycrin

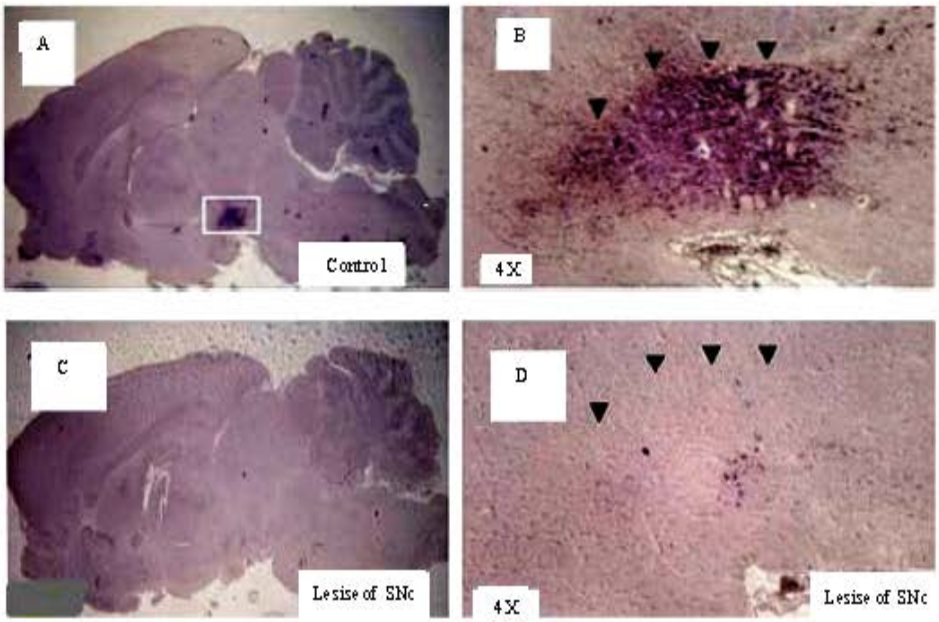

Fig. 1: Histological study about accuracy of lesion of SNc comparison with control groups (negative control and sham); (A) SNc were painted by fuchsine without microscopic magnification in control and sham groups; (B) SNc were painted by fuchsine with microscopic magnification (4X) in control and sham groups; (C) Destroyed SNc in parkinsonian rats did not painted by fuchsine without microscopic magnification and (D) Destroyed SNc in parkinsonian rats did not painted by fuchsine with microscopic magnification (4X); Notes Acute treatments of parkinsonian rats did not improved lesion of SNc

wood-platforms with the steps of 3 and 9 cm were used in this study. The procedure of behavior experiments was as follows:

At the beginning of the test the animal was put on the bench, when it did not move by touch, it received the score of 0.5. Then the right hand of the animal was placed on the wood-platform with the height of 3 cm, if the animal did not take its hand off the platform after at least 10 sec, it received the score of 0.5. Rigidity evaluation was repeated the previous step for the left hand of the animal on the wood-platform with the height of 3 cm and eventually when the animal did not take its hand off from the wood-platform after 10 sec; it was given the score of 0.5.

In the next stage of the procedure the right hand of the animal was placed on the wood-platform with the height of 9 cm, so that any other parts of the animal did not touch the platform, the animal was given 1 score if it did not take it's hand off the platform after 10 sec. Finally the test was repeated in the same way as the previous step for the left hand of the animal on the wood-platform with the height of 9 cm, so that any other parts of the animal did not touch the platform. If the animal did not take its hand off the platform after at least 10 sec, was given another 1 score.

It is pointed out that each of the animals that had full rigidity (PD) was given a total score of 3.5. Scores under 3.5 in Murprogo's Method indicated the recovery of the rigidity and the effectiveness of the treatment. After the Murprogo's test, each animal was decapitated and the brain was removed and kept in a 10% formalin solution. Randomly selected brains were cut on a cryostat as 50 μm thick coronal sections, mounted on glass slides and stained with fuchsine. Sections were examined under a light-microscope to find the accuracy of lesion of the left SNc. Finally, for those animals whose lesion was shown not to be in the SNc, any collected data were discarded.

Statistical analysis: Non-parametrical Kruskal-Wallis, Wilcoxon and One Way Variance Analysis (ANOVA) made comparison between groups and differences with p-values <0.05 were considered significant.

RESULTS

Effects of Aspirin on the rigidity of parkinsonian rats: The groups which received aspirin (30, 60 mg kg^{-1}) had significant differences from the sham, vehicles and positive control with $p<0.05$, except at 0 and 20, 180 and 240 min. Also the group that received aspirin 60 mg kg^{-1} had significant differences from those whose received aspirin 30 mg kg^{-1} $p<0.05$, except at 0, 180 and 240 min (Fig. 2).

Effects of Celecoxib on the rigidity of parkinsonian rats: The groups that received celecoxib (4, 8 mg kg^{-1}) had significant differences from sham, vehicles and positive control with $p<0.01$, except at 0 and 20 and 240 min. Also the group that received celecoxib 8 mg kg^{-1} had significant differences from those whose received celecoxib 4 mg kg^{-1} $p<0.05$, except at 0 and 20 and 240 min (Fig. 3).

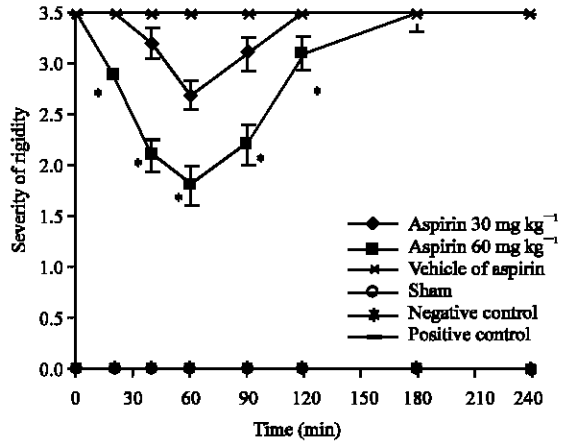

Fig. 2: Comparison the mean of rigidity grade in groups that received aspirin with Sham, negative and positive groups ($p<0.05$)

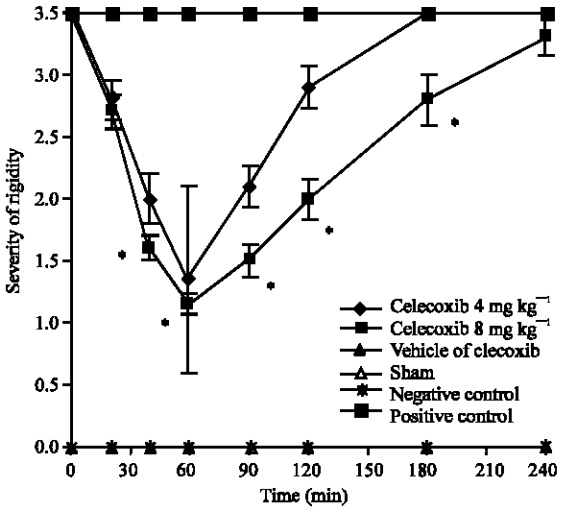

Fig. 3: Comparison the mean of rigidity grade in groups that received celecoxib with Sham, negative and positive groups ($p<0.05$)

Comparison between aspirin and celecoxib on the rigidity of parkinsonian rats: Data analysis in the group which received celecoxib (8 mg kg^{-1}), in comparison with the group which received aspirin (60 mg kg^{-1}) showed the significant differences with $p<0.01$ except at 0, 20 and 240 min which had no significant differences. Celecoxib (4 mg kg^{-1}) has been shown significance differences with aspirin (30 mg kg^{-1}) $p<0.01$, except at 0, 180 and 240 min which had no significant differences.

In addition, celecoxib (8 mg kg^{-1}) differed from aspirin (30 mg kg^{-1}) with $p<0.01$, except at 0 and 240 min which had no significant differences and finally celecoxib (4 mg kg^{-1}) had significant differences with aspirin (60 mg kg^{-1}) with $p<0.05$, at 60 min. The rigidity grades of the parkinsonian rats and their SEM are showed at 0, 20, 40, 90, 120, 180 and 240 (min) in Table 1.

DISCUSSION

Present observations in the present study have shown that the acute use of aspirin and celecoxib caused to improve the rigidity of PD in rat as animal model. Present results showed us that the effective times for recovery of the rigidity were obtained at 60-90 min. According to the results of the study recovery of the rigidity was more seen when the dose of aspirin or celecoxib was increased. Furthermore the recovery of rigidity in the Parkinsonian rats that received celecoxib (as a COX-2 selective inhibitor) was much better than that of receiving aspirin. Our findings suggest that a more important role for COX-2 in the rigidity of PD than that of COX-1.

In agreement with present results, in previous study (Buccafusco *et al*., 1993) has demonstrated that COX-2 and prostaglandin E2 level increased in PD. The previous research (Riechman and Hokin, 1987) suggested that COX-2 caused to increase the level of acetylcholine in the brain to increase by producing of prostaglandin E2 and increasing the expression of cholinergic markers, such as choline acetyl transferase and vesicular acetylcholine transporter protein. It is worthwhile mentioning that prostaglandins have modulatory effects on adrenergic, noradrenergic and glutaminergic transmission (Ito, 1982). In addition, some of the investigations have shown that COX-2 inhibitor impairs the spatial memory through the reduction of acetylcholine level in the brain, but COX-1

inhibitor has not any effect on spatial memory in rats (Rall *et al*., 2003; Sharifzadeh *et al*., 2005). Free radicals and glutamate cause degeneration in SNc, but the inhibition of these agents by antioxidants or glutamate antagonists protects neurons from degeneration (Etminan *et al*., 2002; King *et al*., 1992).

Other anti-inflammatory effects of NSAIDs, possibly, include decreasing production of free radicals and interference with calcium mediated intracellular events (Katzung, 2004).

Neuronal COX-2 over expression may kill neurons in a cell-autonomous manner (Teismann *et al*., 2003) and lead to pathogenic hypothesis for PD (King *et al*., 1992). It is the fact that COX-2 cell-autonomous toxicity may arise from the formation of reactive oxygen species generated during COX peroxidase catalysis of prostaglandin G2 conversion to prostaglandin H2. Electrons donation to COX, co-substrate such as dopamine oxidized to dopamine-quinone. In PD, there is evidence of an increase in oxidative and inflammatory nigral environment that includes the presence of (COX)-immunoreactive activated microglial cells in the substantia nigra. Microglial cells can also produce and release pro-inflammatory cytokines, in particular TNF-α and cytotoxic molecules including ROS and NO (Mladenovic *et al*., 2004). Although such responses are non-specific to lesion type, for example after 6-hydroxy dopamine intrastriatal infusion, there is an acute increase in TNF-α in the striatum (Sánchez-Pernaute *et al*., 2004). In this study we found that COX-2 inhibition by celecoxib and aspirin probably decreased microglial activation or/and the level of TNF-α and free radicals in SNc. In addition, aspirin and ibuprofen significantly attenuated decreases in dopamine uptake caused by glutamate, thus NSAIDs protected neurons against glutamate excitotoxicity *in vitro* (Casper *et al*., 2000). These observations suggest that it is probably the mode of celecoxib and aspirin actions to recover the rigidity, may be contained the inhibition of the enzyme COX-2 and synthesize of prostaglandin E2 and reduction the level of acetyl choline in the brain and probably increase releasing of dopamine from dopaminergic neurons in the brain and protect dopaminergic neurons from glutamate toxicity. In agreements, may be probably other mechanism of aspirin or celecoxib action in the rigidity recovery interference to cellular calcium mediated events may be effective in neurotransmitter releasing and recovery of rigidity, however these suggestions including determination the level of glutamate, dopamine and acetyl choline after administration of NSAIDs in the striatum of parkinsonian rats and/or can changes in striatum neurotransmitters cause to improve the rigidity or not? should be examined carefully in the future experiments.

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