کارگاه‌های آموزشی مرکز اطلاعات علمی

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Original article

Effect of Dexamethasone on Striatal Neurotransmissions in the Rats Subjected to Parkinson's Disease Animal Model

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Abstract

Objective(s)
The aim of this study was to evaluate the effects of dexamethasone on striatal dopaminergic, glutamatergic and gamma amino butyric acid (GABA) ergic neurotransmission in normal and parkinsonian rats.
Materials and Methods
Dexamethasone (0.15, 0.30, 0.60 and 0.8 mg/kg) was administered to normal or parkinsonian rats (i.p.) followed by the analysis of the striatal neurotransmitters concentrations. Additionally, the effect of dexamethasone on the damaged Substantia nigra pars compata (SNc) neurons has been investigated.
Results
Dexamethasone resulted in decreased level of striatum glutamatergic-GABAergic and enhanced dopaminergic neurotransmission in normal and parkinsonian rats. In addition, acute treatment with dexamethasone did not improve the lesion at all.
Conclusion
These findings suggest the new therapeutic mechanism of action for dexamethasone in Parkinson's disease animal model.

Keywords: Dexamethasone, Dopamine, GABA, Glutamate, Parkinson's disease

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Introduction

Parkinson's disease (PD) is a neurodegenerative brain disease in the nigrostriatal pathway of animals or humans. The resulting losses of nerve terminals accompanied by dopamine deficiency in this signaling pathway are responsible for most of the movement disorders affiliated to the disease. Its prevalence or incidence rates increase with age, and more than 2% of the population aged over 60 years and ~ 10–20/100,000 individuals per year are affected by PD. Its diagnosis is based on medical history and a neurological examination, and can be difficult to be proven accurately. Neurodegeneration decreases dopaminergic content in both Substantia Nigra and striatum, which has been ascertained by several neuroimaging evidences. The reduction of ^{18} F-fluoro-L- Dopa, ^{99m}Tc-TRODAT-1, dopamine presynaptic transporter radioligands, and ^{18} F-CIT/FCCIT in the striatum has been demonstrated using positron emission tomography (PET) and single photon emission computed tomography (SPECT) scanning (1, 2). Novel evidences suggest more important roles for inflammatory reactions accompanying the pathological processes seen in many neurodegenerative disorders, including PD (2, 3). Cyclooxygenase (COX) is the first enzyme in the prostaglandin/prostacyclin/thromboxane athway and plays an important role in inflammatory systems. It converts arachidonic acid to prostaglandins and thromboxanes, which are collectively known as its metabolites (4). Three COX isoenzymes, COX- 1, COX-2, and COX-3 (a splice variant of COX-1, which retains intron one and has a frameshift mutation; thus some prefer the name COX-1b or COX-1 variant (COX-1v)) have been identified (5, 6). COX-1 is the constitutive form of COX, and performs a housekeeping function to synthesize prostaglandins, which are involved in regulating normal cellular activities (7). 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. On the other hand, COX converts arachidonic acid (AA, an ω-6 PUFA) to prostaglandin H_2 (PGH_2), the precursor of the series-2 prostanoids. The enzyme contains two active sites: a heme with peroxidase activity, responsible for the reduction of PGG_2 to PGH_2, and a cyclooxygenase site, where arachidonic acid is converted into the hydroperoxy endoperoxide prostaglandin G_2 (PGG_2). The reaction proceeds through H atom abstraction from arachidonic acid by a tyrosine radical generated by the peroxidase active site. Two O_2 molecules then react with the arachidonic acid radical, yielding PGG.

Among the COX isoenzymes, just COX-2 corresponds to inflammatory and degenerative brain disease (5). 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 (6). Increasing evidence suggests that an inflammatory reaction accompanies the pathological processes seen in many neurodegenerative disorders, including PD.

In fact, COX-2 is upregulated during stressful conditions such as cerebral ischemia and is also upregulated by neuronal apoptosis and neurobehavioral defects (8, 9). In addition, the steroidal anti-inflammatory drugs such as dexamethasone can inhibit COX-2 gene expression; the glucocorticoids have widespread effects because they influence in the function of most cells in the body. Glucocorticoids dramatically reduce the manifestations of inflammation. This is due to their profound effects on the concentrations, distribution, and function of peripheral leukocytes and to their suppressive effects on the inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and chemokines on other lipid and glucolipid mediators of inflammation. In addition to their effects, glucocorticoids influence the inflammatory response by reducing the prostaglandin synthesis that results from activation of phospholipase A_2 (3-9).

Hence, steroidal anti-inflammatory drugs such as dexamethasone can inhibit COX-2 gene expression or possible COX-2 upexpressing agents such as TNF-α or CCAAT significantly. Neuroscientists propose

that COX-2 corresponds to inflammatory and degenerative brain disease (10). In cell cultures and animal models, inflammation contributes to the neuronal damage, and anti-inflammatory agents such as dexamethasone or celecoxib have been shown to provide some neuroprotection in animal models of PD (11, 12). Confirming previous studies, administration of steroidal anti-inflammatory drugs (SAIDs) causes the same neuroprotection effects similar to non-steroidal anti-inflammatory drugs (NSAIDs) in PD animal models (13) and also in treatment of PD signs such as rigidity (14, 15).

Furthermore, the anti-inflammatory properties of glucocorticoids are the main reason why they have clinical applications. Many conditions have some component of inflammation as part of their pathophysiology. By administering synthetic versions of these hormones (e.g., prednisone and methylprednisolone) orally or through some other routes, the condition can be better managed.

Many of these conditions are autoimmune diseases or inflammatory conditions with unknown causes. They include, but are not limited to, Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE), and rheumatoid arthritis. Glucocorticoids can also be administered for chronic obstructive pulmonary disease (COPD), immune suppression following organ transplantation, and cortisol deficiency secondary to disease in the pituitary gland or adrenal glands (e.g., Addison's disease).

The study of striatal dopaminergic, glutaminergic or GABAergic interactions has special importance due to the physiological and pathophysiological processes of these systems, such as Parkinson's or Huntington's diseases (14). The critical roles of dopaminergic, glutamatergic, and GABAergic neurotransmissions and their well known interactions in the nigrostriatal pathway and PD led to the some studies such as *in vivo* assays of dopamine, glutamate, and GABA after administration of dexamethasone in normal and PD rat models to investigate the underlying mechanisms for the previously reported improving effect of dexamethasone on PD rigidity (14).

Methods

Chemicals

Dexamethasone, ketamine, and xylazin were purchased from Merck (Germany). Dexamethasone dissolved freely in dimethyl sulfoxide (DMSO), and ketamine and xylazin dissolved in distilled water.

Animals

Male albino Wistar rats (200-250g) were the subjects of the present study. They were housed in groups of eight in stainless steel cages, handled daily and provided with food and water *ad libitum*. A 12 hr light/12 hr dark cycle was maintained, and the animals were tested during the light cycle. These 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 each group contained eight rats (8 animals/group).

Surgery

Each rat was anesthetized separately by injection of 75 mg/kg ketamine combined with 8 mg/kg xylazin i.p. Then, the rats were placed in the stereotaxic instrument. The left substantia nigra pars compacta (SNc) region of the nigrostriatum was targeted at the following coordinates: -4.8 mm posterior and -1.6 mm lateral to bregma and 8.2 mm ventral to the surface of the skull for the left SNc according to the atlas (16) Vehicle (0.2% ascorbic acid). For non-control rats, 6-hydroxy dopamine (6-OHDA) (8 µg in 1 µl in 0.2% ascorbic acid) was infused unilaterally through a 26-gauge stainless steel cannula into the SNc region in order to create hemiparkinsonian rats. Then, the skull was exposed and a hole was drilled through it in the area overlying the right striatum, using the following coordinates with respect to the bregma: A/P + 1 mm; M/L + 3 mm, D/V + 6 mm according to the atlas (16). A guide-cannula lowered into the brain was fixed to the cranium and the incision was closed. Rats were allowed to recover from the surgery for 7–10 days.

Microdialysis procedure

Microdialysis experiments were performed both in normal and SNc-lesioned animals. A microdialysis probe was inserted into the cannula, and the inputs of the probes were connected to a microperfusion pump CMA/102 infusion pump (CMA/Microdialysis, Sweden), which delivered a modified Ringer solution (147 mM NaCl, 1.2 mM $CaCl_2$, 2.7 mM KCl, 1.0 mM $MgCl_2$ and 0.04 mM ascorbic acid) through the probe at a flow rate of 2 µl/min. Ringer solution was then infused for 3–3.5 hr before the baseline samples were collected to obtain stable basal extracellular levels of dopamine, glutamate, and GABA. The microdialysate samples (20 µl) were collected every 20 min and the dialysates were collected for 4 hr. The stress caused by the i.p. vehicle injection, catalepsy evaluation and handling of the rats was not found to alter the extracellular GABA-glutamate-dopamine levels. Microdialysate levels of glutamate-GABA and dopamine were analyzed immediately using reverse-phase high performance liquid chromatography (HPLC).

Histological study

After the experiments, recovery of damaged SNc neurons was evaluated using the histological studies by preparation of 50 µm coronal brain sections as previously described (14). In addition, the location of the probe was determined histologically on serial coronal sections. Only data obtained from rats with correctly implanted probes were included in the results.

HPLC conditions

The electrochemical detection (ECD) system used for dopaminergic determination consisted of a Shimadzu SCL 10-Avp system controller, LC-10AS pump, SIL-10A cooled autoinjector, CT0-10A oven, LECD-6A electrochemical detector and a Gastorr online degasser (ISS, England). System components were used in conjunction with Class VP-5 software (Shimadzu). All samples were injected into a reversed phase Luna 5 µ C18 (2) 250 mm × 4.6 mm column (Phenomenex), which was protected by Krudkatcher disposable pre-column filters (Phenomenex) and SecurityGuard cartridges (Phenomenex).

The fluorescent detection (FLD) system using for GABA-glutamate determination consisted of a Waters 510 pump, 717plus cooled Autosampler, a Hewlett Packard 1046A fluorescent detector, a Waters busSAT/IN module and a Croco-Cil column oven. System components were used in conjunction with Waters Empower software. All samples were injected into a reversed phase Luna 3 µ C18 (2) 150 mm × 2 mm column, which was protected by Krudkatcher disposable pre-column filter and SecurityGuard cartridges.

The mobile phase that was used in the ECD system was composed of a mixture of 0.1 M di-sodium hydrogen orthophosphate/50 µM EDTA (pH 5.4, 1 M OPA) and HPLC grade methanol (36:64). Mobile phase was filtered through Millipore 0.45 µm and vacuum degassed prior to use. Compounds were eluted isocratically over a 20 min runtime at a flow rate of 0.60 ml/min after a 20 µl injection. The column was maintained at a temperature of 30 °C and samples/standards were kept at 4 °C in the cooled autoinjector prior to analysis unless otherwise stated. The glassy carbon working electrode combined with an Ag/AgCl reference electrode (Shimadzu) was performed at +0.8 V unless otherwise specified and the range of the detector was set to 1.

The mobile phase which was used on the FLD system was composed of a mixture of 0.1 M di-sodium hydrogen orthophosphate/50 µM EDTA (pH 5.4, 1 M OPA) and HPLC grade methanol (30:70). Mobile phase was filtered through Millipore 0.45 µm and vacuum degassed prior to use. Compounds were eluted isocratically over a 15 min runtime at a flow rate of 0.1 ml/min after a 20 µl injection. The column was maintained at a temperature of 30 °C and samples/standards were kept at 4 °C in the cooled autoinjector prior to analysis unless otherwise stated. The fluorescent detector was set at an excitation wavelength of 420 nm, an emission wavelength of 480 nm and a PMT gain of 5. GABA/glutamate was identified by their specific retention times as determined by standard injections which were run at regular intervals during sample analysis. Sample peak heights were measured and compared with

standard injections in order to quantify the amino acids.

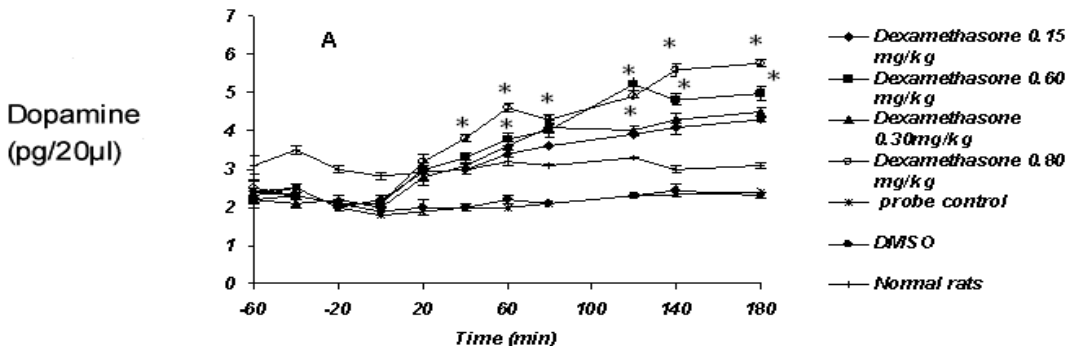
Statistical analysis

The results (described next) are shown as the mean±SEM relative to the basal levels, for 7-8 animals/group. The average concentration of three stable samples from control rats (receiving no drug or vehicle) was considered as the basal levels. Statistical evaluation of the results was performed using one-way analysis of variance (ANOVA) and Student–Newman–Keuls multiple range test, considering the following significant differences: $P< 0.05$.

Results

Mean values for striatal extraneuronal (i.e. microdialysate) concentrations of glutamate in normal and parkinsonian rats before drug-vehicle injection (baseline) were 2.3±0.25 (normal rats) and 2.82±0.35 (parkinsonian rats) ng/20 µl. Mean values for dopamine concentrations were determined as 3.16±0.51 (normal) and 2.1±0.35 pg/20 µl (parkinsonian rats), as well as GABA concentrations 0.129±0.02 ng/20 µl (normal rats) and 0.391±0.06 ng/20 µl (parkinsonian rats) respectively. Varying doses of dexamethasone were observed to change (significantly or not) GABAergic, glutamatergic and dopaminergic neurotransmission in the striatum of normal or parkinsonian rats within the observation period, as depicted in Figure 1. In particular, upon injection of 0.8 mg/kg of dexamethasone, the aforementioned numbers (now averaged from 40-180 min after injection) changed to: (glutamate) 1.78±0.12 and 2.17±0.12 ng/20 µl, (dopamine) 3.54±0.23 ng/20 µl and 3.14±0.21 pg/20 µl, and (GABA) 0.103±0.07 ng/20 µl and 0.121±0.03 ng/20 µl, respectively. The changes caused by dexamethasone on the striatal neurotransmissions of normal or parkinsonian rats indicated that: (i) Significant increase in dopaminergic neurotransmission of parkinsonian rats was observed during the 60 and 140-180 min comparing to normal rats. Furthermore, significant decrease in glutamatergic neurotransmission was observed during the 140-180 period (comparing normal and treated levels). According to the results, a significant decrease in GABAergic neurotransmission during the 40-60 (caused by dexamethasone 0.8 mg/kg) and 140-180 (caused by dexamethasone 0.6 mg/kg) periods, comparing the normal and treated parkinsonian rats' levels were noticed and the result is presented in Figure 1_{A-C}. (ii) All normal rats that received dexamethasone (0.6 and 0.8 mg/kg) were shown a significant ($P< 0.05$) increase in dopaminergic (40-140 min) and decrease in GABAergic (20-80 min, caused by dexamethasone 0.8 mg/kg and 60-180, caused by dexamethasone 0.6 mg/kg) as well as glutamatergic (40-140 min for 0.8 mg/kg or 80-120 min, caused by dexamethasone 0.6 mg/kg) neurotransmission. The corresponding data are shown in Figure1 $_{D-F}$.

Histological results did not show any significant improvement in the damaged SNc neurons resulting from administration of dexamethasone at all (Figure 2).



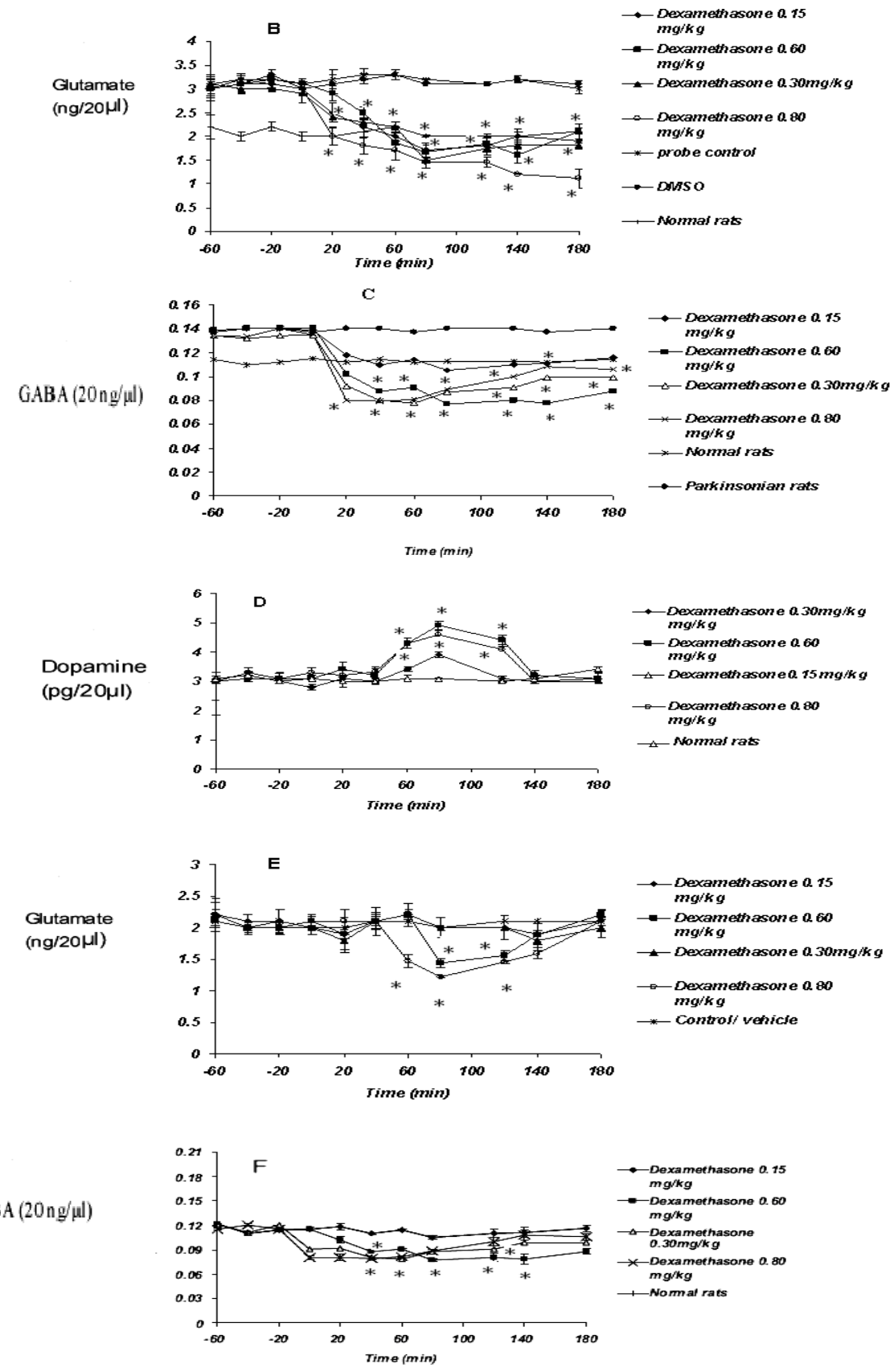


Figure 1. Mean values for striatal (A) dopaminergic, (B) glutamatergic and (C) GABAergic neurotransmission in parkinsonian rats after administration of various doses of dexamethasone. Corresponding results for normal rats are shown in (D), (E) and (F) respectively. The neurotransmission changes in parkinsonian rats caused by dexamethasone were observed to be more significant than normal rats. The significant marker * indicates a significant difference $P< 0.05$ comparing to PD control group.

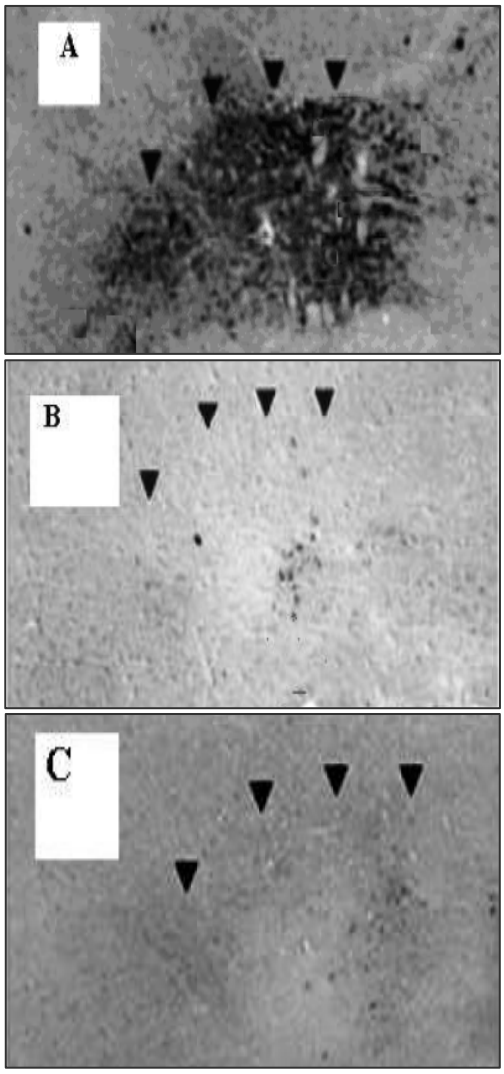


Figure 2. A: Microscopic magnification (4X) of the SNc neurons in normal rats. B: Destroyed SNc before any treatment due to 6OHDA administration. C: Dexamethasone did not improve the damaged neurons caused by 6OHDA at all.

Discussion

This study was intended to explore the important mechanisms of action for dexamethasone as a steroid in glutamatergic, GABAergic and dopaminergic neurotransmission in the striatum of normal and parkinsonian rats. Additionally, this study showed that acute dexamethasone administration did not have any improving effect on damage SNc.

It is reported that inflammation and its mediators such as prostaglandins (PGs) have an important role in neurotransmitter release (12, 14). These reports suggested that inflammation causes increased levels of acetylcholine in the brain via production of PGE2 and increases in expression of cholinergic markers, such as choline acetyl transfrase and vesicular acetylcholine transporter protein. It was also reported that prostaglandins have modulatory effects on adrenergic, noradrenergic and glutaminergic transmission, specially PGE2, and prostaglandin synthesis inhibitors induced increases in the blood pressure via increases in the release of the catecholamine; for example using large doses of glucocorticoids in humans may cause insomnia, euphoria and increase the intracranial pressure (14, 17).

Moreover, glucocorticoids, namely cortisol, have multiple functions related to metabolism and regulation. They raise blood glucose levels through breakdown of fat and muscle protein, increasing insulin resistance in tissues, and other processes. They also inhibit bone formation, raise the blood pressure, and suppress inflammatory processes as part of their additional regulatory function. Stress is a major cause of glucocorticoids release.

Another line of evidence suggests that parkinsonian patients when confronted with a stressful event are able to overcome their immobility for a short period of time. This is proposed to be due to a release of catecholamines from adrenal medulla or activation of central sympathetic noradrenergic neurons. It has been also reported that glucocorticoids can increase adrenaline production by exerting a stimulatory action on two of the enzymes that regulate catecholamine synthesis viz. tyrosine hydroxylase (the rate limiting enzyme) and phenylethanolamine N-methyl transferase (6-9, 11, 15, 16). One of the other proposed mechanism for the above observations is regarding to neuronal COX-2 over gene expression which may kill neurons in a cell-autonomous manner and leads to pathogenic hypothesis for PD (17-20). It also suggests that COX-2 cell-autonomous toxicity may arise from the formation of reactive oxygen species generated during COX peroxidase catalysis of prostaglandin G_2 conversion to prostaglandin H_2. Electron donation to COX facilitates dopamine oxidation to dopamine-quinone. In PD, there is evidence of an increased level of

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. These may inhibit neurotransmission release in striatum region. Dexamethasone probably protects these events and increases dopamine release which can also act as a key point in the recovery pathway of PD.

The results were also in confirmation with previously published literatures showing that COX-2 nor COX-1 or COX-2 gene expression inhibition did not repair SNc damaged neurons acutely or chronically (14, 17).

The above observations show a good therapeutic potential for dexamethasone in PD signs recovery. It should be added that in the literature there are some explanations for neuronal damage caused by corticosteroids. It has been shown repeatedly that under certain conditions glucocorticoids exacerbate different types of neurological defects (2-4). As the hippocampus is a major target for neuronal degeneration in the brains of patients with AD, and as it is richly endowed with GRs, it is also a principal target site for glucocorticoids.

Neurotoxic challenges induced by the oxidative stressors Aß and glutamate, two neurotoxins that have been implicated in AD (6-9, 11, 15, 16, 18-20), are enhanced by pretreatment of the hippocampal neurons with glucocorticoids. However, in controversy of our results (acute study) it should be stated that there is evidence that steroidal compounds like dexamethasone can protect dopaminergic neurons against PD (18-20). Indeed, that was a chronic study and it is possible that the difference observed due to mentioned above-reasons.

Further experiments are necessary in order to clarify the role of anti inflammatory agents such as dexamethasone in other striatal neurotransmissions.

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