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Review Article

Neuroprotective Effects of Guanosine Supplementation in Experimental Models: A Systematic Review

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ABSTRACT
Guanosine (GUO) is an endogenous guanine nucleoside to which several neuroprotective and neurotrophic effects have been attributed in experimental *in vitro* and/or *in vivo* models of central nervous system (CNS) diseases, including ischemic stroke, Alzheimer's, Parkinson's disease, spinal cord injury, nociception and depression. The objective of this work is to systematically review the neuroprotective effects of guanosine in experimental models in the CNS. The research was conducted through PubMed, Science direct, Scopus, Cochrane Library and SciELO (Scientific Electronic Library Online) and databases, where a number of relevant articles were found. Central nervous system (CNS) astrocytes release guanosine extracellularly, that has trophic effects. In the CNS, extracellular guanosine (GUO) stimulates mitosis, the synthesis of trophic factors and cell differentiation, including neuritogenesis, is neuroprotective and reduces apoptosis due to various stimuli. In this work we demonstrate that guanosine has a neuroprotective effect, through the survey of data that we carry out.
Key words: Guanosine, Neuroprotective effect, Central nervous system.

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INTRODUCTION

The Central Nervous System (CNS) presents the greatest cellular diversity of the organic systems of the human body, in addition to being associated with extremely complex activities that involve the individual's relationship with the environment, affective life and intellectual activity. Combined with its morphological and functional complexity, the CNS is home to several disabling diseases, such as the neurodegenerative diseases of Alzheimer and Parkinson; tumors and neurological disorders such as schizophrenia, autism, among others.[1]

With the increase in Brazilian longevity and the high prevalence in the elderly population, neurodegenerative diseases should soon increase their relevance among public health problems in Brazil, as they represent an important cause of mortality in Brazil and worldwide, they are also responsible for considerable rates of neurological morbidities. They are multifactorial diseases. Their treatments are only symptomatic, which highlights the importance of studying new therapies. Therefore, some studies have been carried out to elucidate the role played by guanosine in the CNS.[2]

There are different situations, such as traumatic injuries, neurodegenerative diseases or stroke events, which can compromise neuronal function, thus interrupting the dynamic balance of the brain. In all of these cases, brain repair is necessary and neuroregenerative mechanisms exist to restore neuronal function. Neuroprotection can be defined as the mechanisms that try to reduce the secondary side effects of a wide variety of internal or external aggressions that require the display of specific mechanisms for the survival of neural cells.[3]

Guanosine is a purine nucleoside derived from nitrogenous guanine base, with important functions in cellular metabolism and a neuroprotective role in response to diseases or degenerative lesions, in the CNS, exposure to hypoxia conditions associated with hypoglycemia (*in vitro* ischemia) increases extracellular concentration of guanosine approximately four times.[3]

The extracellular effects of purines based on guanine or guanine derivatives have been shown mainly in the CNS and these effects are related to the modulation of the glutamatergic system, the main exciting neurotransmission system in the brain, the neurotransmitter glutamate.[4]

Several studies point to a possible neuroprotective role of guanine derivatives against disorders of the glutamatergic system (excitotoxicity) and also to physiological processes involving this system.[4] Thus, since several nutrients exert a neuroprotective action, the acquisition of these nutrients is extremely relevant for reducing the risk of developing neuronal disorders. Although purine derivatives are very promising compounds for the treatment of CNS disorders, there is no treatment efficient dressing

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that has been proven effective to date. This review discusses the effects of guanosine on the CNS, with the guiding question "Does Aguanosine have a neuroprotective effect on the CNS?". Guanosine (GUO) has been shown to act as a neuroprotective agent against glutamatergic excitotoxicity by increasing glutamate uptake and decreasing its release. We highlight the importance of guanosine in protecting the central nervous system by activating its receptors and intracellular signaling mechanisms.

MATHERIALS AND METHODS

The present study comprises a systematic review of the literature, developed based on stages previously constituted of search, identification, selection and eligibility strategies. A literature review was carried out using the Science Direct, United States National Library of Medicine (PubMed), Cochrane library and Scielo databases between 2009 and 2018. The database search was performed using the terminologies registered in the Science Descriptors (DeCS) created by the Virtual Health Library (VHL).

The descriptors used in the search were: Guanosine; neuroprotective effect; central nervous system, to detect all studies that have analyzed the effects of supplementation in experimental models with guanosine, using the Boolean operator "AND" to combine the descriptors. The search for studies was carried out independently by two expert evaluators in the context discussed, through the titles, abstracts or both, resolving discrepancies through a subsequent consensus meeting. The screening of the studies was carried out based on the title and the summary and soon after the publication was fully reviewed and compared.

Experimental studies that supplemented *in vivo*, *in vitro* models of guanosine, including its neuroprotective action and reduction of pathological symptoms through behavioral analyzes, were included. And the following exclusion criteria were considered: 1) Review articles; 2) Books; 3) Experimental models other than mice or cell culture; 4) And in the absence of a control group (the control group had to be comparable to the group supplemented with guanosine); 5) The experimental model tested should induce neuroprotection with guanosine infusion; 6) The *in vitro* models used should be cells from mice or cells of human lineage.

In addition to the inclusion and exclusion criteria mentioned above, the study's eligibility criteria for inclusion in this systematic review were applied: All articles must be indexed and published in renowned journals with considerable impact factors; All models used in the studies must present the clinical signs or symptoms of the neuroprotective action of guanosine; animals must be treated with guanosine. Statistical grouping was not considered in this review due to methodological heterogeneities between studies, as the authors evaluated different methods and cell lines in addition to different dosages of guanosine between studies. Therefore, meta-analyzes could not be performed on the data accessed.

The studies analyzed in this systematic review show high levels of heterogeneity in important aspects such as the agent inducing the neuroprotective action of guanosine, the duration of treatment with guanosine and the behavioral tests used. The studies used different compounds to simulate neuronal damage and they all work through different mechanisms of action. As with guanosine extracts, these compounds were administered in different doses and through different routes. In addition, the studies reported in this systematic review used different behavioral tests and neurochemical analyzes, which also reinforce the heterogeneity of the studies as shown in Table 1.

RESULTS

Studies differ in some ways. As for the sex of the animals used in the studies, most of them were male wistar rats (12), female wistar rats (2), female Swiss mice (2), male Swiss albino mice (1) and rats (1). The agents used to induce neuroprotection were guanosine and fluoxetine (2), guanosine (10), guanosine and ammonium acetate (1), guanosine, guanine, N-omega-methyl ester of L-arginine (L-NAME) (2), guanosine and guanine (1), guanosine and reserpine (1) and guanosine and guanine´5 monophosphate (1). For behavioral analysis, studies used MTT recuction assay (5), immunoblotting analysis (1), protein measurement (1), walking task (1), locomotor rating scale (1), activity rotaroad test (1), passive avoidance assessment of locomotor (1), glutamate uptake (1), immunohistochemistry assay (2), open field test (4).

The 18 articles were carefully analyzed and summarized in terms of authorship, year of publication, type of lesion, experimental groups, dosage and main findings.

DISCUSSION

Depression

Depression and stress-related disorders affect approximately 17% of the population, resulting in enormous personal suffering, as well as social and economic burdens. The neurobiology underlying depression is not yet fully identified, but it is believed to be the result of cellular abnormalities that interact with environmental factors.[22]

Guanosine is a purine nucleoside that occurs naturally in the central nervous system, exerting trophic effects. Given its neuroprotective effect, the potential of guanosine as an antidepressant has recently been examined. The study sought to investigate the effects of chronic guanosine treatment on the tail suspension test (TT), open field test and adult hippocampal neurogenesis. The results suggest that the antidepressant effect of treatment with chronic guanosine is associated with an increase in neuronal differentiation, reinforcing the notion that this nucleoside may be an endogenous mood modulator.[6]

However, the ability of this nucleoside to neutralize behavioral and biochemical changes induced by acute stress has not been evaluated in female mice, as depression is more prevalent and has a worse clinical outcome in women. The study sought to investigate the protective effect of this nucleoside against oxidative damage and the stress coping response assessed in the FST. ARS has been proposed as a model that triggers biochemical changes in the mouse brain that can be detrimental to the function of the CNS. Among these changes, an increase in glutamate release and an imbalance in oxidative / antioxidant parameters have been reported in rodents. This resulted in increased production of ROS and / or inefficiency in antioxidant systems leads to oxidative stress and is implicated in several psychiatric illnesses, including major depression.[5]

Taking into account that the hippocampus plays a fundamental role in memory, mood regulation, it is not surprising that numerous studies evaluate whether the neurogenesis of the adult hippocampus is altered in psychiatric disorders. Stress is a risk factor for a variety of disorders mood and anxiety, including depression and post-traumatic stress disorder, which can manifest years after the stressful event.[23] Behavioral studies have shown that guanosine produces anxiolytic substances and amnesic effects, possibly related to its ability to modulate the glutamatergic system. In fact, several studies have shown that the stress-induced reductions in hippocampus cell proliferation and / or neuronal differentiation are linked to the development of depressive symptoms.[24]

The study by Deng *et al.*[24] says that the neurogenesis of the hippocampus in humans is affected by several neurological disorders, including depression, epilepsy, cerebral ischemia, Alzheimer's disease and Parkinson's disease, many of which are associated with cognitive decline. According to Duman *et al.*[22] in their recent studies and others, they demonstrated that the chronic administration of an antidepressant,

Table 1: A summary of studies on the effects of Guanosine supplementation in CNS experimental models found in PubMed, Science direct, Cochrane Library and SciELO databases, showing authorship, year of publication, type of lesion, experimental groups, dose regimen and main conclusions.

AUTHORSHIP / YEAR OF PUBLICATION	NEUROPROTECTIVE EFFECT	EXPERIMENTAL MODEL	GROUP REGIME AND EXPERIMENTAL DOSE	MAIN FINDINGS
Bettio Luis E.B. *et al*. 2014[5]	Prevents neuronal oxidative damage and anti-depression	Adult female Swiss mice (subjected to behavioral changes in forced swim test and hippocampus antioxidant imbalance induced by the acute containment stress protocol (ARS).	4 groups: Vehicle not stressed; Not stressed + guanosine; Stressed vehicle; Stressed + guanosine. The number of rats per group was 7 to 9. Fluoxetine was added as a positive control in the forced swim test (FST) and open field test in another set of experiments. Guanosine and fluoxetine were dissolved in distilled water and administered orally. (po) at a dose of 5 and 10 mg / kg, respectively, 1 h before the procedure of the acute containment stress protocol (ARS).	The study showed that Guanosine and fluoxetine prevented the ARS-induced immobility time increase in FST. ARS, guanosine and / or fluoxetine did not alter locomotor activity. In addition, guanosine protected the hippocampus of mice against ARS-induced lipid peroxidation.
Bettio Luis E. B. *et al*. 2016[6]	Anti-depression	Adult female Swiss mice (brains were removed and processed for immunohistochemical analysis))	Analysis 1 (Effect of chronic treatment with guanosine): vehicle (control) group received distilled water by p.o. route (10 mL / kg), Guanosine 5 mg / kg p.p. Analysis 2 (Effect of chronic treatment with fluoxetine): Vehicle, fluoxetine 10 mg / kg - Total, dorsal and ventral (hippocampal neuronal differentiation). Analysis 3 (hippocampal cell proliferation as assessed): Vehicle, guanosine (5 mg / kg, p.o.). 5–8 animals used per group. Guanosine and fluoxetine were dissolved in distilled water and administered orally at a dose of 5 and 10 mg / kg, respectively, once a day for 21 days and on day 22 they were submitted to TST and open field testing.	It has been shown that mice treated with guanosine (5 mg / kg, p.o.) over a 21-day period showed a reduction in immobility time in the TST and was not accompanied by changes in locomotor activity. The immunohistochemical analysis of NeuroD revealed a significant increase in the number of immature neurons in the hippocampal DG of mice treated with guanosine, so it is understood that guanosine can be a good modulator of neuronal differentiation in the hippocampus.
Chang R. *et al*. 2008[7]	Protection against stroke	Male wistar rats (stroke model induced by middle cerebral artery occlusion - MCAo).	2 groups: Eight animals with MCAo were randomly divided into two groups of four. One group received guanosine and the other, a vehicle. Two additional animals that had all surgical procedures except MCAo served as simulated controls and did not receive guanosine. Guanosine (8mg / kg) was administered intraperitoneally or saline (vehicle control) daily for 7 days.	The study suggests that guanosine prolonged the mice's survival and decreased both neurological deficits and tissue damage resulting from MCAo. These data are the first to demonstrate that guanosine protects neurons from the effects of CGOD, even when administered 5 hr after stimulation and is neuroprotective in experimental strokes in rats.
Cittolin-Santos GF *et al*. 2017[8]	Neuroprotection against glutamatergic excitotoxicity	Adult male wistar rats received an intraperitoneal (ip) injection of a 60 mg / kg ouGUO vehicle, followed 20 min later by an ip vehicle injection or 550 mg / kg of ammonium acetate	4 groups: Ammonium acetate (150-750 mg / ml) was dissolved in distilled water and administered via ip injection. Concentrations of ammonium acetate solutions were adjusted to achieve the desired dose by injecting 3 mL / kg of body weight, as previously described. Guanosine was dissolved in 0.1 mM NaOH and used as a pre-treatment 20 min before the injection of ammonium acetate. A vehicle solution of 0.1 mMNaOH was used as a control. Both solutions were adjusted to pH 7.4. The guanosine solutions and the vehicle solution were administered i.p. injection at a dose of 2 mL / kg of body weight.	GUO dramatically reduced the lethality rate and the duration of the coma. Oxidative stress in the cerebral cortex and increased glutamate uptake by astrocytes in slices of the brain compared to animals that received a vehicle before the administration of ammonium acetate. This study provides new evidence on the mechanisms of purines derived from guanine in its potential modulation of the glutamatergic system, contributing to the neuroprotective effects of GUO in a rodent model for acute ammonia poisoning.

Dal-Cim T *et al.* 2011[9]	Neuroprotective role of guanosine in rats hippocampus slices submitted to OGD.	Rat hippocampus slices subjected to OGD (oxygen / glucose deprivation) of adult male wistar rats	3 groups: The hippocampus slices were subjected to three different conditions: control - hippocampus slices were kept in Ringer's Buffer Krebs for 15 min; OGD - slices of the hippocampus were subjected to OGD buffer for 15 min; OGD and reoxygenationgroup - slices of the hippocampus were submitted to 15 min for OGD and followed by 2 hr of reoxygenation.	The neuroprotective effect of guanosine involves increasing glutamate uptake, which is modulated by BK channels and activation of the PI3K pathway. In addition, the neuroprotection caused by guanosine depends on increased expression of the phospho-Akt protein.
Dal-Cim T *et al.* 2013[10]	Protection against ischemic brain injury	Hippocampus slices of adult Wistar rats (Oxygen / glucose deprivation and reoxygenation (OGD).	Analysis I (Quantification of the mean fluorescence obtained in CA1): Basal, Guanosine (GUO, 100 lM) with or without Charibdotoxin (100 nM) or DPCPX (250 nM) (CA1). Analysis II (Quantification of the mean fluorescence obtained in CA1): Basal, Guanosine (GUO, 100 lM) in the presence or not of LY294002 (LY 10 lM) or PD98059 (PD 25 lM). (CA1). Analysis III (Densitometric quantification of p65): Basal, Guanosine (GUO, 100 lM in the presence or not of Charibdotoxin (100 nM), LY294002 (LY 10 lM), DPCPX (250 nM) and PD98059 (PD 25 lM). binding protein - TATA used to control the nuclear fraction (Nucleo and cytosol). Analysis IV (Densitometric quantification of INOS): Pre-incubated slices (NAC, 5 mM) or 1400W (20 or 50 lM), NAC or 1400 W was maintained during the periods of OGD and reoxygenation. Analysis V (MTT reduction and Glutamate uptake expressed): Basal, GUO (100 lM) in the presence or not of carbidotoxin (100 nM), LY294002 (LY 10 lM), DPCPX (250 nM) or PD98059 (PD 25 lM). Analysis V1 (MTT reduction): Basal, GUO (100 lM) in the presence or not of pertussis toxin (500 ng / mL), OGD, OGD GUO, OGD PTX GUO. Analysis VII (Glutamate reduction): GUO (100 lM) in the presence or not of DPCPX (250 nM, adenosine A1 receptor antagonist) or PD98059 (PD 25 lM). In both groups the slices were incubated for 15 min in ischemic buffer and reoxygenated for 2 hr. And GUO was added during reoxygenation.	Guanosine has been shown to modulate the function of the adenosine receptor by activating MAPK / ERK, thus providing neuroprotection of hippocampal slices subjected to OGD by a mechanism that implies: preventing depolarization of the mitochondrial membrane, reducing oxidative stress, regulating inflammation by inhibition of nuclear factor kappa B and induced synthesis of nitric oxide and promotion of glutamate uptake, possibly acting to protect against ischemic injury.
Hansel G. *et al.* 2015[11]	Protection against focal cerebral ischemia	Permanent focal cerebral ischemia induced in adult male wistar rats	4 groups: Sham Saline (SS), Sham GUO (SG), Saline Ischemia (IS) and GUO Ischemia (IG). The guanosine dose was chosen based on the dose-response curve. All groups received 1 ml / kg i.p. administration of drugs immediately, 1, 3 and 6 hr after surgery.	It was observed that the ischemic event increased the levels of positive Iba-1 cells and pro-inflammatory cytokines and decreased the levels of IL-10 (an anti-inflammatory cytokine) in the periphery of the lesion. Treatment with guanosine attenuated changes in these inflammatory parameters and also reduced the volume of infarction, the incorporation of PI and the number of cells positive for FJC, improving functional recovery.

Gerbatin R.R. *et al*. 2016[12]	The effect of guanosine in neurological damage induced by TBI	Male wistar rats with 120 days of glass received a single dose of guanosine (7.5 mg / kg, intraperitoneally (ip) injected 40 min after fluid percussion injury (IPF).	4 groups: animals per cage (polypropylene), 41 × 34 × 16 cm W × D × H, 1394 cm2) with the floor covered with autoclaved chips under controlled conditions (12: 12-hr light-dark cycle, lights on at 7:00 am, 24 ± 1°C, 55% relative humidity) on a ventilated shelf with access to water and food. It evaluated the effect of guanosine on TBI-induced neurological damage.	Protected against exploratory and locomotor deficiencies 8 hr after the injury. Lateral cortex, glutamate uptake, Na + / K + -ATPase, glutamine synthetase activity and changes in mitochondrial function. The inflammatory response and cerebral edema were also reduced by this nucleoside, in addition to guanosine protected against neuronal death and caspase-3 activation, this study suggests that guanosine plays a neuroprotective role in TBI and can be explored as a new pharmacological strategy.
Giuliani P. *et al*. 2012[13]	Protects neurons from Induced neurotoxicity and brain slices of damage induced by hypoxia / hypoglycemia	Adult male Wistar rats received intraperitoneal (i.p.) injection of guanosine in guanine (GUA) and N-omega rats. The methyl ester of l-arginine (L-NAME)	10-15 rats / group: in which the rats received different treatment: saline (control group); 100 mg / kg of L-NAME i.p. 30 min before training (pre-training) or immediately after training (post-training); 4-8 mg / kg of GUO p.o. 30 min before training or 15 min before L-NAME; 4-8 mg / kg of GUA p.o.30 min before training or 15 min before L-NAME and 15 min before L-NAME after training (post-training).	Guanosine (4 and 8 mg / kg) administered pre-training impaired retention in the passive avoidance task and was unable to prevent the amnesic effect caused by 100 mg / kg of nitro-l-arginine methyl ester (L-NAME). Guanine (4 and 8 mg / kg), which by itself did not modify the latency to pass the passive avoidance task, when administered pre-training 15 min before L-NAME prevented, in a dose-dependent manner, the amnesic effect NOS inhibitor.
Giuliani P. *et al*. 2012[14]	Antiparkinsonian	Male rats received Guanosine (GUO), guanine (GUA) and N-omega. The methyl ester of l-arginine (L-NAME)	10-15 rats / group: in which the rats received different treatment: saline (control group); 100 mg / kg of L-NAME i.p. 30 min before training (pre-training) or immediately after training (post-training); 4-8 mg / kg of GUO p.o. 30 min before training or 15 min before L-NAME; 4-8 mg / kg of GUA p.o.30 min before training or 15 min before L-NAME and 15 min before L-NAME after training (post-training).	Guanosine (300 μM) protected SH-SY5Y neuroblastoma cells when they were exposed to 6-OHDA, promoting their survival. Guanosine reduced 6-OHDA-mediated activation of p-38 and JNK. In addition, the nucleoside potentiated the initial increase in the phosphorylation of the anti-apoptotic kinase Akt and the increase in the expression of the anti-apoptic Bcl-2 protein induced by 6-OHDA.
Giuliani P. *et al*. 2012[15]	Neuroprotection related to inhibition of apoptosis, cytotoxicity, glutamatergic neurotransmission and formation of protein aggregates, as well as stimulation of glutamate uptake, synaptogenesis and tissue repair	Male adult wistar rats received intraperitoneal injection of guanosine	5 rats / groups: I) rats were treated with an ipinjection of 1ml of saline solution (control group) to evaluate the endogenous amount of GUO and its derivatives in plasma and tissues; II) rats were treated with an ipinjection of 1ml of 2,4,8 or 16mg / kg GUO combined with 0.05% of [3H] GUO (15Ci / mmol) to evaluate the plasma concentration of GUO and its metabolites at 7.5,15,30,60 and 90min after ipinjection (5rats / dose); III) rats were treated with ipinjection of 1ml of 8mg / kg of the GUO [3H] GUO mixture and were then sacrificed to evaluate levels of GUO and its metabolites in the tissues at the same time periods reported above (5rats / time point).	The levels of radioactivity in the plasma increased. Guanosine was widely distributed in all tissues analyzed in the present study, with almost twice the usual levels. In addition, guanine levels increased dramatically in all organs. Enzymatic analysis of plasma samples showed the presence of soluble purine nucleoside phosphorylase, a key enzyme in the purine rescue pathway and nucleoside catabolism.
Shucui Jiang *et al*. 2007[16]	Reduction of apoptosis and associated inflammation with restoration of spinal function	Adult female Wistar rats were administered systemic guanosine (8 mg / kg per day, ip) for 14 consecutive days, starting 4 hr after moderate spinal cord injury in rats	2 groups: 22 rats from 4 hr after surgery, they received daily intraperitoneal (ip) injections of 8 mg / kg of guanosine or the same volume of saline containing 0.001 NNaOH[5] for 2 weeks. On day 7 after the injury, an animal in the saline group was euthanized by a severe bladder infection.	Reduction of inflammation, resulting in the protection of axons, oligodendrocytes and neurons and the inhibition of cell death by apoptosis.

Jiang S., 2008[17]	Remyelination after chronic spinal cord injury	Adult female wistar rats (Moderate spinal cord injury was induced by crushing exposed cords)	Analysis I (OFWT score): guanosine-treated; vehicle-treated Analysis II (Mean luxol fast blue stained): guanosine; vehicle control; Unoperated animals. Analysis III (Quantitative assessment of immunostaining (NG2 + cells) and (NG2 + Brdu): vehicle-control, guanosine. The rats received daily intraperitoneal (i.p.) injections of 8 mg / kg of guanosine or the same volume of 0.001 N NaOH saline solution [31] for 2 weeks, preoperatively. After spinal cord injury, recovery was assessed weekly for 35 days.	Improvement in remyelination after systemic administration has been demonstrated due to the effect of guanosine / guanine on the proliferation of adult progenitor cells and their maturation in myelin-forming cells.
Molz S., 2011[18]	Protection against excitotoxicity and cell death caused by excess glutamate (Neurodegenerative diseases)	Hippocampus slices of adult Wistar rats (Incubated with glutamate)	Analysis I (Cellular viability): guanosine (GUO 30, 100 and 300 μM), Glu, GUO 30 μM + Glu, GUO 100 μM + Glu, GUO 300 μM + Glu. Analysis II (Glutamate released): Control, LY294002 (30 μM), 1 mM Glutamate (Glu) in the presence or absence of 100 μM GUO, LY294002 + GUO + Glu. Analysis III (Cellular viability): Glu, GUO + Glu, LY294002 + GUO + Glu, LY294002. Analysis IV (Immunodetection of phosphorylated and total p-Akt, t-Akt in hippocompal slice): Control, GUO 30min, GUO 60min, GUO 90min. Analysis V (Immunodetection of phosphorylated GSK3bSer9in hippocampal slice): Control, GUO, LY294002, LY294002 + GUO. Analysis VI (LY294002 prevents GUO-induced up-regulation of GSK3b at Ser9): Control, GUO, GUO 30min + GLU, GUO100μM + Glu, GUO 300μM + Glu. Analysis VII (Immunodetection of iNOS in hippocampal slice): C, GUO, LY294002, Glu, GUO + Glu, LY294002 + GUO + Glu. Analysis VIII (Cellular viability): SNAP (1 mM), GUO + Glu, Glu, SNAP + Glu, SNAP + GUO + Glu. When present, GUO was pre-incubated for 30 min before the addition of glutamate. LY294002 was added to the incubation medium 15 min before GUO and maintained during the pre-incubation period.	The results of this study show that guanosine protects the hippocampus slices by a mechanism that involves the PI3K / Akt / GSK3β (Ser9) pathway and the prevention of glutamate-induced glutamate release. In addition, guanosine also reduces glutamate-induced iNOS by a PI3K / Akt-independent mechanism.
Massari CM *et al*. 2017[19]	Antiparkinsonian	Male Swiss albino mice administered reserpine and an Experimental model hemiparkinsonism was induced in rats by unilateral injection of 6-OHDA in the medial forebrain bundle	3 groups: Vehicle (0.1% acetic acid solution), reserpine (1 mg / kg, sc), GUO (3, 5, 7.5 or 10 mg / kg; po). The vehicle was administered twice every 48 hr. Reserpine was dissolved in 0.1% acetic acid for subcutaneous (s.c.) administration. GUO was dissolved in saline. 6-OHDA was dissolved in saline containing 0.05% ascorbic acid. DL-serine 2- (2,3,4-trihydroxybenzyl) hydrazide and 3,4-Dihydroxy-L-phenylalanine hydrochloride (dissolved in saline for intraperitoneal (ip) administration. GUP was administered 20 min before behavioral test and 24 hr after the last reserpine injection.	Oral administration of GUO has been shown to antagonize reserpine-mediated catalepsy and to reduce mandibular tremor movements in rats injured by 6-OHDA. In addition, at 5 and 7.5 mg / kg, GUO inhibited L-DOPA-induced dyskinesia in rats chronically treated with a pro-dopaminergic agent. Its therapeutic potential may be effective not only to reverse parkinsonian motor deficits, but also to reduce dyskinesia induced by PD treatment.

Moretto M. B. *et al*. 2009[20]	Neuroprotection in a model of ischemia hypoxia	Male Wistar rats after seven days of age received GUO intraperitoneal injection (7.5mg / kg)	2 groups: (1) Protocol 4, immediately after and 24 hr and (2) 5 protocol, immediately after and 48 hr (protocol 4 to 5) after HI the [3H] glutamate taken by hippocampal slices determined 3 days after the hypoxic insult. Data are expressed as mean ± SEM of eight to ten animals in each group.	GUO has a protective effect on glutamate uptake but three doses were required according to protocols 6 to 8 fact that the first dose has the same effect when administered once, 3 or 6 h after the insult. This shows that Guo administration schedule is crucial in achieving these results. Moreover, only three doses were able to prevent the reduction of glutamate concentration that capture is essential to protect Guo against excitotoxicity glutamatoa early intervention Guo repeated doses prevented the decrease in absorption caused by glutamate HI.
Oleskovicz S.P. *et al*. 2008[21]	Guanosine-induced neuroprotection in rats slices of the hippocampus subjected to oxygen-glucose deprivation	Male adult wistar rats (slices of the hippocampus were subjected to 15 or 60 min of OGD, followed by 2 h of reperfusion)	4 group: Control + drug 15 min OGD15 min; OGD + drug; 15 min OGD + R + GUO; 15 min OGD + R + GUO + drug Test compounds were incubated during the OGD period only, or during the OGD and reperfusion period.	It has been shown that the neuroprotective effect of guanosine has not been altered by the addition of adenosine receptor antagonists, nucleoside transport inhibitors, glutamate receptor antagonists, glutamate transport inhibitors and a non-selective Na (+) channel blocker and Ca (2+). However, in a Ca (2 +) free medium, guanosine was ineffective. Nifedipine (Ca2 + channel blocker) increased the neuroprotective effect of guanosine. The assessment of intracellular signaling pathways associated with guanosine-induced neuroprotection showed the involvement of PKA, PKC, MEK and PI-3 K pathways.

including a selective inhibitor of the reuptake of 5-HT or norepinephrine, positively regulates neurogenesis in the hippocampus of adult rodents.

The over-regulation of neurogenesis could block or reverse the effects of stress on neurons in the hippocampus, which include negative regulation of neurogenesis, as well as atrophy. The possibility that the cAMP signal transduction cascade contributes to the regulation of neurogenesis by antidepressants is supported by previous studies and recent work.

Disorders in hippocampal neurogenesis may be involved in the pathophysiology of depression and it has been argued that an increase in the generation of new nerve cells in the hippocampus is involved in the mechanism of action of antidepressants. Adult Wistar rats were treated with fluoxetine (10 mg / kg) 1 hr, daily for 5 (subchronic) or 28 days (chronic). Cell proliferation and neurogenesis were analyzed using the 5-bromo-deoxy-2-uridine markers, Ki-67.

A significant behavioral effect was found after 28 days of fluoxetine administration. However, no behavioral improvement was demonstrated after acute and subchronic treatment with fluoxetine. We also demonstrate that chronic antidepressant treatment increases cell proliferation, as well as neurogenesis in the dentate gyrus, using Wistar rats. In the development of antidepressants, neurogenesis can serve as an important parameter to examine the efficacy and mechanism of action of new drugs.[22]

In conclusion, the development of new treatments for depression is based on the identification of neural substrates and mechanisms underlying their etiology and pathophysiology. The heterogeneity of depression indicates that its origin may be in the dysfunction of multiple brain regions. The neurogenesis of the adult hippocampus as a candidate mechanism for the etiology of depression and as a substrate for antidepressant action. Current evidence indicates that the neurogenesis of the adult hippocampus may not be a major contributor to the development of depression, but it may be necessary for some of the behavioral effects of antidepressants.[25]

Brain stroke

Stroke is the second leading cause of death in industrialized countries and the leading medical cause of adult acquired disability. Rapid intervention after the onset of a stroke can limit neurological damage and improve the recovery of the patient's functioning.[26]

Chang *et al*.[7] shows that after using combined glucose and oxygen, the administration of guanosine (100 μM), a purine nucleoside, significantly reduced the proportion of apoptosis. To determine whether guanosine was also neuroprotective *in vivo*, the middle cerebral artery (MCAo) was occluded in male Wistar rats and guanosine (8 mg / kg) was administered intraperitoneally or saline (control vehicle) daily for 7 days. Guanosine prolongs survival and decreased both neurological deficits and tissue damage resulting from MCAo. These data are the first to demonstrate that guanosine protects neurons from the effects of CGOD even when administered 5 hr after stimulus and is neuroprotective in stroke.

According to Garcia *et al*.[27] most brain injuries that develop after an artery is occluded evolve from an initial stage of "ischemic injury" (probably reversible) to a heart attack or an area where most neurons are located. Makes it necrotic. There is a predictable progression in the development of neuronal necrosis after permanent arterial occlusion. The causes of the lesion's progression are not known; however, therapeutic interventions that start in the first 1 to 2 hr after arterial occlusion can alter histopathological responses to this form of injury.

The study by Deng *et al*.[24] investigated whether late administration of GUO improved long-term functional recovery after stroke. Late

administration of GUO did not reduce the volume of the infarction or affect neurological function on the 7th day after the stroke; however, it improved functional recovery from the 14th day after the stroke, when compared to the vehicle group. GUO significantly increased the number of BrdU + and BrdU + / DCX + cells in the subventricular and subgranular zone at all times analyzed, the number of Brdu + / NeuN + cells in the peri-infarction region on days 14 and 28 after stroke and microvascular density in the peri-infarction region on day 28 after stroke compared to the vehicle group. In addition, BDNF and VEGF levels in the ipsilesional brain were significantly elevated Figure 1.

Gerbatin,[12] evaluated the effect of guanosine on TBI-induced neurological damage. The findings showed that a single dose of guanosine (7.5 mg / kg, intraperitoneally (ip) injected 40 min after fluid percussion injury (IPF) in rats protected against locomotor and exploratory impairment 8 h after the injury. The treatment also protected against neurochemical damage to the ipsilateral cortex, glutamate uptake, Na + / K + -ATPase, glutamine synthase activity and changes in mitochondrial function. The inflammatory response and cerebral edema were also reduced by this nucleoside. In addition, guanosine protected against neuronal death and caspase activation 3. Therefore, this study suggests that guanosine plays a neuroprotective role in TBI and can be explored as a new pharmacological strategy.

Experimental models of ischemic stroke contribute to our understanding of the events that occur in the ischemic and reperfused brain. One of the main approaches developed to treat acute ischemic stroke falls under neuroprotection. Despite the failure of most neuroprotective drugs during the past two decades, there is a good chance that effective neuroprotectors will soon be available with the help of improved pre-clinical testing and clinical study design Figure 2.

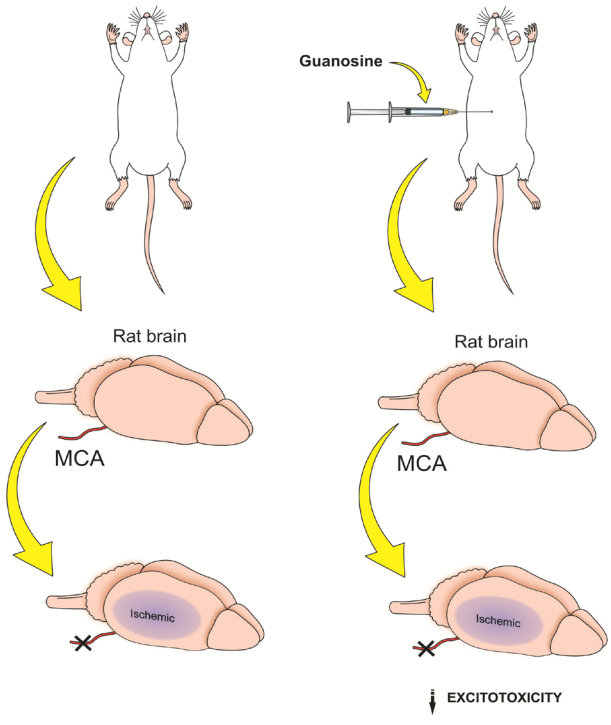

Figure 1: GUO significantly increased the number of BrdU + and BrdU + / DCX + cells in the subventricular and subgranular zone at all times analyzed, the number of Brdu + / NeuN + cells in the peri-infarction region on days 14 and 28 after stroke and microvascular density in the peri-infarction region on day 28 after stroke compared to the vehicle group.

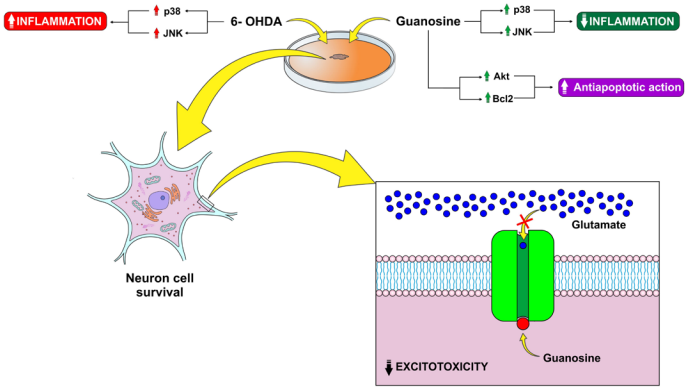

Figure 2: Despite the failure of most neuroprotective drugs during the past two decades, there is a good chance that effective neuroprotectors will soon be available with the help of improved pre-clinical testing and clinical study design.

Neurotoxicity induced by glucose/oxygen

Guanine-based purines exert several extracellular effects including modulation of glutamatergic activity, trophic effects on neural cells and behavioral effects. Current evidence suggests that guanine-based purines modulate glutamatergic parameters, such as glutamate uptake by astrocytes and synaptic vesicles, seizures induced by glutamatergic agents, response to ischemia and excitotoxicity and are capable of affecting learning, memory and anxiety. In addition, guanine-based purines have important trophic functions that affect the development, structure or maintenance of neural cells.[4]

In a study by Dal-Cim *et al.*[28] He showed that guanosine protects the hippocampus slices submitted to 15 min of OGD followed by 2 h of re-oxygenation and this effect involves the activation of the BK channels. In addition, OGD and OGD followed by reoxygenation promoted a reduction in glutamate absorption. Guanosine preventing such a reduction via BK and PI3K channels activating the pathway, as demonstrated by the pharmacology blockade with selective inhibitors. In addition, guanosine increases Akt phosphorylation in slices submitted to OGD and reoxygenation, an effect also prevented by pharmacological blockade of BK channels. Guanosine-50-monophosphate (GMP) is shown to be neuroprotective against neurotoxicity induced by glutamate or oxygen / glucose deprivation and also against apoptosis in slices of the hippocampus. However, in this study Molz *et al.*[18] demonstrated that high extracellular GMP concentrations (5 mM) reduced cell viability in slices of the hippocampus brain.

The toxic effect of GMP was not blocked by dipyridamole, an inhibitor of nucleoside transport, nor imitated by guanosine, suggesting a mode of extracellular action to GMP that does not involve its hydrolysis to guanosine. GMP-dependent cell damage was not blocked by P1 purinergic receptor antagonists, nor altered by adenosine A1A A2A receptor agonists. Blocking the AMPA or NMDA ionotropic glutamate receptors, but not KA or metabotropic glutamate receptors, reversed GMP-induced toxicity. GMP (5 mM) induced decrease in glutamate uptake in hippocampus slices, which was reversed by DL-TBOA.

Parkinson's disease

Parkinson's disease (PD) is a pathological condition characterized by a progressive neurodegeneration of dopaminergic neurons with the consequent reduction of the dopamine content to black substance. The neurotoxin 6-hydroxydopamine (6-OHDA) is widely used to mimic the neuropathology of PD in experimental models *in vivo* and *in vitro*.[29]

In the study by Giuliani *et al.*[14] guanosine (300 μM) protected SH-SY5Y neuroblastoma cells when they were exposed to 6-OHDA, promoting their survival. Guanosine reduced 6-OHDA-mediated activation of p-38 and JNK. In addition, the nucleoside potentiated the initial increase in phosphorylation of the anti-apoptotic kinase Akt and the increase in the expression of the anti-ap-optic Bcl-2 protein induced by 6-OHDA. Another study looked at the ability of guanosine to protect neuronal PC12 cells from toxicity induced by 1-methyl-4-phenylpyridinium (MPP +), the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which mediates selective damage to dopaminergic neurons and causes irreversible symptoms similar to those of Parkinson's in humans and primates. The results showed that MPP +-induced apoptosis of PC12 cells was significantly prevented by pretreatment for 3 h with guanosine. Furthermore, guanosine attenuated the collapse of MPP +-induced mitochondrial transmembrane potential and prevented subsequent activation of caspase- 3, thus protecting dopaminergic neurons against damage induced by mitochondrial stress.[30]

Current PD medications treat symptoms; none prevents or delays the degeneration of dopaminergic neurons. It is understood that guanosine is neuroprotective in a recognized *in vitro* model of PD, suggesting that it could represent a potential new pharmacological tool to be studied in the therapeutic approach to PD.[31]

CONCLUSION

Together, the data suggest that animals treated with guanosine had neuroprotective action on the CNS, which resulted in a reduction in neuronal loss. The use of guanosine improved the results of behavioral tests in experimental models of neuroprotection. For this reason, in addition to its low incidence of side effects, it seems reasonable to assume that the use of guanosine can improve the quality of life of individuals affected by neurodegenerative diseases.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ABBREVIATIONS

GUO: Guanosine; **CNS:** Central nervous system; **DeCS:** Science Descriptors; **VHL:** Virtual Health Library; **L-NAME:** N-omega-methyl ester of L-arginine; **ARS:** Acute containment stress protocol; **OGD:** Oxygen / glucose deprivation; **TT:** Suspension test; **MCAo:** Middle cerebral artery.

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