MODULATION OF THE SYSTEM IN SEROTONINERGIC PARKINSON'S DISEASE: THERAPEUTIC APPLICATIONS IN BASIC AND CLINICAL RESEARCH

Jean Carlos Souza Silva,[1] Antônio William do Nascimento Fernandes,[2] Dayane Pessoa de Araújo[3]

ABSTRACT
Serotonin, also called 5-hydroxytryptamine is a neurotransmitter synthesized from dietary tryptophan regulatory having high potential in human tissues. 5-HT can act as a neurotransmitter in nerve fibers of fixed catalyst homeostatic responses and central nervous system can control cognition, emotion and motor behavior. The present study is an investigation of the main applications and intervene[1]Therapeutic ções described in publications about the serotonergic modulation in patients with Parkinson's disease in different stages as well as the experimental animal studies induced parkinsonism. The study leads to an update of the main therapeutic targets as serotonin transporter, serotonin receptor tissue, among others.

Keywords: Serotonin; 5-HT, Parkinson's disease; Neurodegeneration.

INTRODUCTION

Serotonin also known as 5-hydroxytryptamine is synthesized biogenic amine from the amino acid tryptophan and was initially described as a neurotransmitter, but currently many effects are attributed to this molecule being capable of acting from the central nervous system by the tissue and peripheral organs (WU et al., 2019). Depending on the mechanism of action, it can be classified as a hormone, neurotransmitter or mitogen and is able to regulate many behavioral and physiological processes in animals (WU et al., 2019; MOHAMMAD-ZADEH; MOSES; GWALTNEY-BRANT, 2008). Increasing evidence suggests that Parkinson's disease (PD) not only affects the dopamine system (POLITIS; LOANE, 2011). Apart from the loss of dopaminergic neurons, it is also observed progressive degeneration of noradrenergic and serotonergic neurons (LI et al., 2018).

Serotonergic neurons are located in the nuclei of the brainstem raphe. Their projections are subdivided into two types: Rostral with sharp projections to the forebrain, innervating the hypothalamus, basal ganglia, amygdala, cingulate gyrus, medial cerebral cortex and of the hippocampus and the flow projections extending to the brainstem flow and spinal cord (BERGER; GRAY; ROTH, 2009).

[1] Biologist and Student Multicenter Program Graduate Physiological Sciences at the University of Rio Grande do Norte, Mossoró / RN.
[2] Nurse and Student Multicenter Program Graduate Physiological Sciences at the University of Rio Grande do Norte, Mossoró / RN.
[3] Professor of the Postgraduate Program in Physiological Sciences and Nursing Graduate Course, State University of Rio Grande do Norte, Mossoró, RN, Brazil. Email: dayanepessoa@gmail.com

The serotonergic system is correlated to various functions, including cognition, emotion and motor behavior. Thus, drastic changes in the functioning and homeostasis of this neurotransmitter can contribute to the development of diseases associated with motor and non-motor activity (POLITIS; NICCOLINI, 2015). The degeneration results in serotonergic neurons in the limbic function defects also damaging emotion and cognition patients(TEISSIER; SOIZA-REILLY; CASPAR, 2017).

Evidence from studies in animals and humans suggest that striatal serotonergic terminals may contribute to the development of dyskinesias induced by levodopa (DIL) promoting a non-physiological release of dopamine.

Studies using animals, molecular methods, and post-mortem human models show changes in the serotonergic system in the progression of PD striatal and extra-striatal regions. Postmortem brains of PD patients show a decrease in striatal 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) (KISH et al., 2007). Findings suggest that striatal dopaminergic innervation depletion provide positive feedback in increased striatal serotonergic innervation, both in humans and in animals (MAEDA et al., 2005) since these neurons can convert L-DOPA into DA, even in a deregulated way, postmortem studies and diagnostic imaging should take into account the chronic use of L-DOPA by patients (CARLSSON et al. 2007).

Mice with mutations LRRK2 gene knockout show significant reductions in 5-HIAA levels at 8 and 12 months compared to 4 months old (CREED, et al. 2019). Some patients diagnosed with idiopathic PD may show significant reductions in the concentrations of neurotransmitter DA, NA and 5-HT. And the level hypothalamic sub-regional and the most affected (SHANNAK et al., 1994).

Serotonin dysfunction has a direct impact on non-motor symptoms of PD including depression, fatigue, binge eating, body weight fluctuations and visual hallucinations. target with pharmacological therapies in the serotonergic system may alleviate these symptoms (POLITIS; LOANE, 2011). Serotonin is presented as a promising neurotransmitter in the understanding of early symptoms associated and poorly understood in PD, for example, sleep impairment, anxiety, hallucinations, and alteration of gastrointestinal motility (MOREIRA-JUNIOR, 2019).

This paper presents a literature review of the most recent work involving studies of the serotonergic system in PD, by focusing the basic and clinical research, and associated

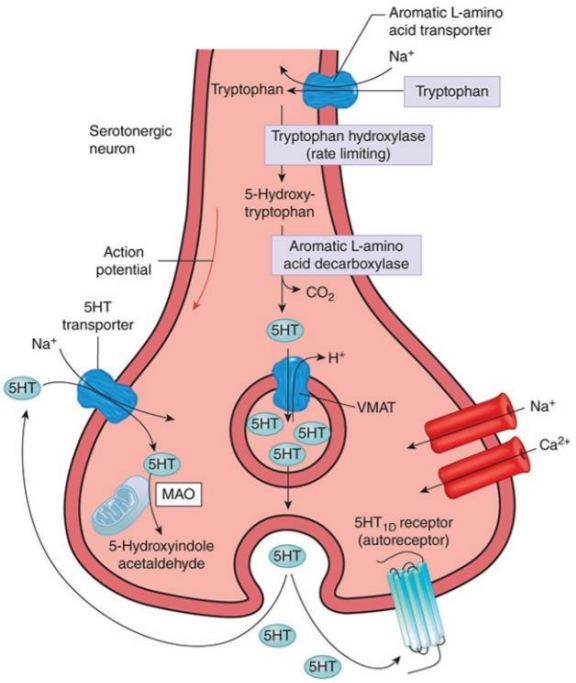
psychopathology. The study begins with a description and conceptual aspects Morphophysiological about the synthesis and secretion of serotonin by nerve fibers, and then describes the findings from recent studies involving experimental parkinsonism and preclinical and clinical studies with patients with the disease.

2 SYSTEM SEROTONERGIC: SYNTHESIS AND METABOLISM 5-HT IN NERVE FIBERS

Tryptophan enters the serotonergic fibers by L-aromatic amino acid transporter in symport with sodium into the fiber as shown in Figure 1. Subsequently, undergoes the action of tryptophan hydroxylase enzyme that adds one hydroxyl group at carbon 5 and converts tryptophan -o L-5-hydroxytryptophan. This first step of the reaction acts as a controller of neurotransmitter synthesis target being a limiting enzyme molecule synthesis. The decarboxylase enzyme aromatic L-amino acid removes the carboxyl grouping the L-5-hydroxytryptophan converting it finally in serotonin or 5-hydroxytryptamine. The newly synthesized serotonin is stored in cytoplasmic vesicles by the vesicular monoamine transporter that translocates in antiporter with H + ions exit into the cytosol. The vesicles will be stored in the synaptic terminals as the excitation of the fiber transduces the action potential to the synaptic terminals and will cause the opening of voltage regulated Na + and Ca2 + channels that will promote the influx of these ions and facilitate vesicular fusion with the plasma membrane of neurons. presynaptic cells on the face facing the synaptic cleft, thus causing the exocytosis of 5-HT molecules in the synaptic cleft to perform their synaptic function (AZMITIA, 2007; BERGER; GRAY; ROTH, 2009; DAVID; GARDIER, 2016; BARRETT et al., 2019).

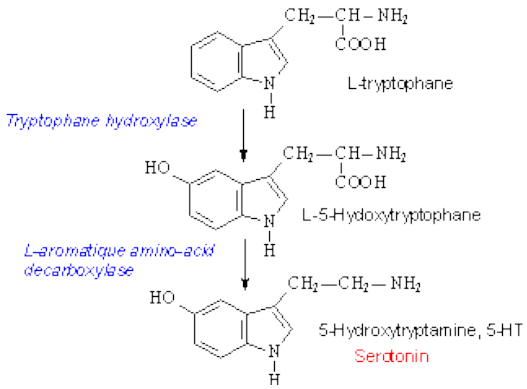
The self 5-HT1D receptor shown in figures 1 and 2, serves to regulate the synaptic cleft vesicle fusion, acting as serotonin secretion regulatory molecule. When the concentration of 5-HT in the slot alters this receptor can signal the presynaptic neuron and to change it regulates itself to secrete more 5-HT (Azmitia, 2007). The serotonin transporter (SERT) is a symporter Na + and 5-HT in the synaptic cleft with function recapture serotonin from the synaptic cleft into the cytosol of the presynaptic neuron for subsequent storage / recycling vesicular inside or metabolized by MAO B hidroxindol-5-acetic acid (5-HIAA) (BERGER GRAY; ROTH, 2009; 2019 BARRETT et al.).

Figure 1 - Synthesis, secretion, and metabolism of serotonin in the presynaptic serotonergic fibers from the amino acid tryptophan



Source: Barrett et al. (2019).

Figure 2 - Reaction stages of the amino acid tryptophan to serotonin and converting enzymes involved in the process



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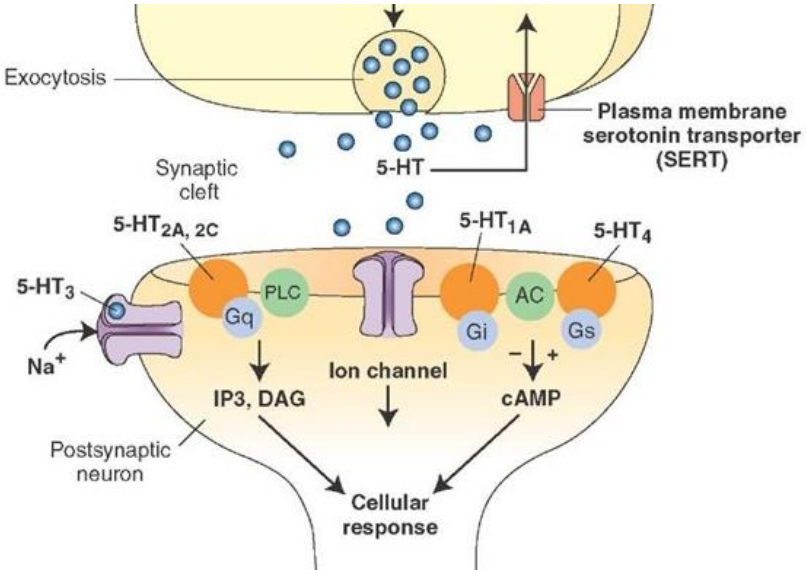
Accessed on 12/02/2019.

In the synaptic cleft, 5-HT molecule can bind different receptors and trigger signaling pathways are distinct. The range of serotonin receptors is broad, since their families reported subgroups. Figure 3 shows the different receptor subtypes that can excite neurotransmitter and its intracellular signaling cascades that are triggered at different subtypes. Of setoroninérgicos receptors described to date, just family of 5-HT3 receptors are channel type, the others are

metabotropic receptors coupled to G protein, can be Gq, Gi or Gs (NICHOLS NICHOLS, 2008; BERGER & GRAY; ROTH, 2009; DAVID; GARDIER, 2016; BARRETT et al., 2019).

Figure 3 - synaptic cleft and interaction of synaptic terminals of presynaptic serotonin neurons and serotonergic receptors of the postsynaptic fiber



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3 THERAPEUTIC INTERVENTION IN serotonergic SYSTEM IN PARKINSON'S DISEASE RESEARCH BASIC

3.1 Serotonin Transporter (SERT)

The binding of 3-amino-4- (2-dimethylaminomethyl-fenilsulfaril) -benzonitrila (DASB) decreases after 6-OHDA lesions in the striatum, cortex and hippocampus of rats subjected to experimental models of parkinsonism. Chronic treatment with L-DOPA preserves the availability of SERT in healthy and injured hemisphere compared to the control group of animals (WALKER ET AL., 2019).

The striatal serotonergic fibers are hiperinervadas to the lesioned striatum and have potential dopamine synthesis and secretion as a compensatory action of the resultant of the striatal dopamine deficit lesion with the neurotoxin 6-OHDA (MAEDA et al., 2005).

Administration of 3,4-methylenedioxy-N-methamphetamine in nonhuman primates damage serotonergic terminals affect the dopaminergic neurons and enhances the

neurotoxicity of MPTP. The prior application of MDMA potentiated the MPTP-induced Parkinsonism and associated dopaminergic lesion. Monkeys submitted to MDMA administration can develop so parkinsonian more pronounced deficits and to a lesser period of time. Symptoms significantly affected was the tremor and abnormal posture were significantly aggravated. MDMA induced a decreased availability of serotonin transporter and induced a decreased availability of dopamine transporter to a lesser extent (MILLOT et al., 2020).

3.2 Serotonin receptors.

Immuno-histological approaches and biochemical detected impairment implications of the serotoninergic system in the DP, with a deep specific reduction layer serotonergic input in the layers II and V / VI of the prefrontal cortex (PFC) in old mice expressing synuclein mutant A53T. The changes in cytoarchitecture fibers characterized by swollen axons and axonal varicosities in all layers CBP. The animals had increased levels of kinesin family member 1a and the vesicular monoamine transporter 2. Along with increased levels of tryptophan hydroxylase mRNA 2 in the raphe nuclei and 1b receptor overexpression of serotonin in the PFC as a compensatory action on the deficit dopamine induced in the model (WIHAN et al., 2019).

The stimulation of 5-HT1A receptor by astrocytes rotigotine, a drug used to treat parkinsonism, can induce neuroprotection by inducing the production of antioxidant molecules and neurotóficos factors. The rigotina acts by binding to 5-HT1A receptors and dopamine astrocytes, being able to increase the number of astrocytes and expression of metallothionein (MT)-1,2 striatal astrocytes, and hence attenuate dopaminergic neurodegeneration. As also able to significantly inhibit dopaminergic neurotoxicity induced by 6-hydroxydopamine (6-OHDA). suggesting thus, possible therapeutic applications in the prevention of dopaminergic neuronal degeneration (ISOOKA et al., 2020).

5HT4 receptor agonists have potential as therapeutic drugs useful for the treatment of cognitive deficits in PD. The dopaminergic neurodegeneration MPTP can directly influence the GABAergic neurons in the black substance pars compact and serotonergic neurons in the raphe nuclei Median, and thus result in hippocampal dysfunction. Prucalopride Administration of Velusetrag and in models of experimental Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice, failed to restore the extinction

of contextual fear, stimulating the cAMP / PKA / CREB in the hippocampal dentate gyrus (ISHII; KINOSHITA; MUROI, 2019).

Injuries to the neurotoxin 6-OHDA induced impairment of working memory. Activation of the 5-HT4 receptor BIMU-8 and the locking agonist antagonist GR113808 injected at the side habenula (LHb) proved able to recover the working memory in rats lesioned with the neurotoxin, and improve monoamine levels. The number of neurons positive for the 5-HT4 receptor significantly increased in injured mice, suggesting the 5-HT4 receptor as a potential pharmacological target (YUAN et al., 2019).

The dopamine depletion and treatment with L-DOPA are unable to significantly enhance the expression of 5-HT2C receptors, 5-HT4 and 5-HT6 striatum. However, the lesion with the neurotoxin 6-OHDA considerably increases the mRNA levels of 5-HT 1B throughout the striatum. Treatment with L-DOPA also significantly increases the expression of the 5-HT1B the striatum with low levels of dopamine, plus a slight increase in 5-HT 1B expression in unlesioned striatum. The increased 5HT 1B expression correlated with increasing severity of dyskinesia induced by treatment with L-DOPA (PADOVAN-NETO, et al., 2019).

The 5-HT6 receptor in dorsal hippocampus showed effects in the regulation of anxiety associated with PD. The intra-dHip injection joint 5HT6 WAY208466 receptor agonist and their SB258585 antagonist resulted in an increase in the percentage of time spent in the central area in the open field test, the percentage of open arms entries and the open arm time in the test plus maze high, indicating that induced anxiolytic effects. When administered alone, the WAY208466 produced anxiolytic responses in injured mice, while SB258585 produced anxiogenic effects in the same group (LIU et al., 2019).

Studies suggest that 5-HT6 receptor is involved in the regulation of memory to the experimental animals induced parkinsonism. The lesion with 6-OHDA induces impairment of hippocampal-dependent working decreasing DA in the striatum memory, medial prefrontal cortex, dorsal hippocampus and amygdala. The intra-DH injection WAY208466 5-HT6 receptor agonist and antagonist SB258585 increased the accuracy of choice and decreased the number of changes in the head. In addition to increasing levels of DA and NA in the medial prefrontal cortex (LIU et al., 2016).

The 5HT-6 receptor in the dorsal hippocampus also establishes connection with the regulation of anxiety associated with PD. Mice induced experimental parkinsonism by 6-

OHDA treated WAY208466 when produced anxiolytic responses, while SB258585-treated produced anxiogenic effects, but increased levels of DA in the posterior hippocampus, ventral hippocampus and amygdala. When treated with both drugs increased the percentage of time spent in the central area in the open field test, the percentage of open arm entries and time in the open arm maze test in high cross (LIU et al., 2019).

THERAPEUTIC INTERVENTION APPLIED TO THE SYSTEM IN SEROTONERGIC PARKINSON DISEASE TRANSLATIONAL MEDICINE AND CLINICAL RESEARCH

Serotonin transporter

PD patients exhibit changes in Serotonin Transporter binding (SERT). The binding of SERT is reduced symmetrically with whole brain and brainstem these patients, not limited to the late stages of the disease (ALBIN et al., 2007).

Postmortem studies indicate the loss of serotonergic neurons in PD. DASB studies using a radioligand for SERT associated with positron emission tomography prove PD patients have reduced binding to the SERT (ALBIN et al., 2007). The positron emission tomography in vivo also shows changes in serotonergic terminals, damage to a degree nonlinear viariável, which continues from the initial stage of the disease (POLITIS; LOANE, 2011).

A cross-sectional study of patients with idiopathic PD, patients with Ala53Thr autosomal dominant mutation (A53T; 209G → A) in the α-synuclein gene (SNCA) demonstrated that patients with pre-motor symptoms A53T SNCA show a reduction in binding potential to DASB nuclei in the ventral and dorsal raphe, caudate, putamen, thalamus, hypothalamus, amygdala, and brainstem. While the carriers of SNCA A53T PD, there extension to regions of the hippocampus and cingulate anterior cingulate posterior insula, frontal cortex, parietal, temporal and occipital. The evidence suggests that molecular SERT images may be in view of practical applicability premotor PD pathology in vivo (WILSON et al., 2019).

The rate of decline of the availability of serotonin transporter in a two-year interval in PD patients newly diagnosed using 123ioflupano-fluoropropyl-carbomethoxy-3-beta-4-iodo-feniltropano (123I-FP-CIT) observes the reduction of 16.6 ± 20.9% (mean ± SD) in the

serotonin transporter availability, from the beginning to the two years of monitoring groups, with 34.1% of patients showed a decreased availability of serotonin transporter (PASQUINI et al., 2019). The use of pramipexole was also reported to induce adaptive potential negative regulation of citalopram binding to the SERT (BERGHAUZEN-MACIEJEWSKA et al., 2016).

Patients with PD and Huntington Korea showed optical density and pattern of innervation TH decreased and increased SERT. The innervation of striated 5-HT is slightly increased in both diseases. The increase of striatal 5-HT observed in PD can be explained by neural by a compensatory feedback mechanism of dopaminergic denervation (BÉDARD et al., 2011)

Mutation of LRRK2 gene carriers manifest DP has no significant increase in serotonin transporter binding in the hypothalamus, striatum and brain stem. The striatal binding of VMAT is presented in asymmetric reduction in these patients. The serotonergic innervation compensatory changes that precedes the onset of PD engine. The enhancement of serotonergic innervation could contribute to differences in clinical PA by mutation of LRRK2, such as the emergence of non-motor symptoms and changes in the long term response to levodopa (WILE et al., 2017).

Serotonin receptors

Dopamine acts as a selective endogenous agonist at the 5-HT2A receptor, acts to promote the activation and internalisation. The T307 and K429 residue in receptor cytoplasmic segments are critical for the signaling process, with important functional selectivity of 5HT2A receptors and may be subject to future drug therapies (SOMAN; BHATTACHARYA, PANICKER, 2019). As AD is released unregulated way of serotonin terminals in animal models of experimental parkinsonism (CARTA et al., 2010) data suggest that excessive dopamine in the post-synaptic serotoninergic terminal resulting from treatment with L-DOPA may result on activation of postsynaptic 5-HT receptors and play adverse effects of treatment (SOMAN; BHATTACHARYA, PANICKER, 2019). O 5-HT2A receptors may also play an important role in the treatment with L-dopa in patients with PD.

The primavanserina is an inverse agonist at 5HT2A receptors is currently suggested as treatment of psychoses of PD. Patients with schizophrenia and schizoaffective disorder with hallucinations and delusions refractory non-responders to clozapine (largely gold standard

accepted for resistant psychotic symptoms) showed improvement in negative symptoms and social behavior of patients, but more controlled studies comparing clozapine and pimavanserina in refractory schizophrenia are required (NASRALLAH; FEDORA; MORTON, 2019).

Huot and Kwan (2019) suggest potential applications of the 5-HT3 receptor antagonists with selective blockade in the treatment of psychosis in PD. However, these promising results need to be confirmed by larger randomized studies. Many selective antagonists of the 5-HT3 receptor are available, but the number of published works focused on the application of these compounds in preclinical and clinical trials psychosis in PD still lacking.

PSYCHOPATHOLOGY ASSOCIATED WITH PARKINSON DISEASE: DEPRESSION AND ANXIETY

The pathophysiology of depression in PD is uncertain. Many morphological and physiological changes are found in depressed patients with PD. Dopamine, serotonin and norepinephrine neurotransmitters can be found altered in PD (RYAN; EATMON; Slevin, 2019). PD patients have a high rate of depression, especially mild to moderate levels. made from patients with depressive and nondepressed PD studies showed that 59% of patients studied level mild depression, moderate or severe according to the score obtained in the Hamilton Depression Rating Scale (HAMD). The levels of dopamine and serotonin were all significantly reduced in the group of patients depression DP (LIAN et al., 2019).

Antidepressant therapies show benefits in patients with PD. Yet still further comparative studies are needed in patients with depression DP (RYAN; EATMON; SLEVIN, 2019).

Already in PD anxiety disorders may be related neurochemical changes in experimental models of parkinsonism induced by 6-OHDA. After administration of the neurotoxin, the animals showed similar symptoms as anxiety reduced mobility, lower scores in open field test, the anxiety-like behavior in the elevated plus maze and in contextual fear conditioning test. The results corroborate with the neurochemical analyzes, the levels of the neurotransmitters dopamine and norepinephrine are reduced striatum, prefrontal cortex and amygdala. While serotonin is reduced in the striatum and prefrontal cortex, but increased in the amygdala. Anxiety-like behavioral changes may be the result of dysregulation of

neurotransmitter systems in brain areas involved with anxiety, such as the amygdala, prefrontal cortex, and striatum (VIEIRA et al., 2019).

Functional neuroimaging studies show that the severity of anxiety correlates negatively with the structural covariance between the left striatum of subregions and contralateral caudate nucleus of patients with idiopathic PD. The severity of anxiety measured by the Beck Anxiety Inventory (BAI) was associated with reduced structural covariance between dorsal right caudate nucleus, ventrolateral prefrontal cortex ipsilateral nucleus accumbens and left dorsolateral prefrontal cortex ipsilateral. The data suggest that the reduced inter-hemispheric cooperation implies loss in emotional regulation (OOSTERWIJK et al., 2018).

In experimental models of progressive parkinsonism induced in mice by reserpine in low doses, was found a neuronal damage extending beyond the dopaminergic system, also affecting serotonergic neurons. The immunoreactivity of 5-HT decrease in hippocampal subfields (CA1 and CA3) and the medial prefrontal cortex (mPFC). The changes in immunoreactivity with 5HT start early in the course of progressive parkinsonism in rats induced by repeated low-dose model of reserpine (LEAL et al., 2019).

SEROTONINERGIC SYSTEM PARTICIPATION IN NOKICEPTION IN PARKINSON'S DISEASE

Pain in PD may be classified as nociceptive or neuropathic pain. The transient receptor potential vanilloid 1 (TRPV1) has great contribution, being highly expressed in patients with PD and its lock may relieve pain in PD. The TRPV1 sensitization was maintained for 5-HT / 5-HT3AR and 5-HT downward in rostral ventromedial medulla (RVM) is upregulated after injection of 6-OHDA injection in C57BL / 6J mice the dorsal horn of the spinal cord and subnucleus caudal trigeminal analog. Hyperalgesia is blocked by depletion of 5-HT descending RVM (LI et al., 2019).

Noradrenergic and serotonergic systems has a fundamental role in the regulation of motor responses and nociceptive circuits in PD, modulating the opioid system and the glial response to the spinal cord. reuptake inhibitors NA and 5-HT (Desipramine and citalopram) showed efficacy against neuronal impairment in the locus coeruleus and nuclei magnos raphe against behavioral immobility against mechanical hyperalgesia inhibited via analgesic descending prevented the hyperalgesia in the ipsilateral hindpaw to injury and prevent

changes in the circuits of the spine in the animal model induced Parkinsonism. While not interfering directly on nigral lesions (CAMPOS et al., 2019).

The inhibition of hypersensitivity to pain in rats lesioned with 6-OHDA was observed with the use of NE reuptake inhibitor and 5-HT duloxetine after injection of neurotoxin (CAO et al., 2016). Preserve the noradrenergic and serotonergic systems can regulate nociceptive circuits during PD, not interfering directly in nigral lesions but modulating the opioid system and the glial response to the spinal cord.

CONCLUSION

Understand the processes underlying neurodegenerative diseases has been challenging over the years. The literature review presented in this work brings together the most pathological, anatomical and physiological findings of PD current related to the participation of the serotonergic system in the pathogenesis and therapy in PD from basic research in models of experimental parkinsonism induced to preclinical and clinical studies which are currently published in databases. These findings seem to relate many of the mechanisms of neurodegeneration not disclosed in PD and the functional correlations of serotonergic neurons. Understanding changes in the serotonergic system may help guide future studies in identifying a treatment and cure for this debilitating, heterogeneous disease that reduces the quality of life of many patients.

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