BREATHING AND ITS STIMULATORY RESPONSES IN PARKINSONISM: REPERCUSSIONS FOR PHYSIOTHERAPY

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ABSTRACT

This study addresses respiratory and motor impairments in an experimental reserpine-induced model of parkinsonism in rats. The role of chronic hypoxia due to diminished ventilation in the development and course of neurodegeneration is addressed. An attempt was made to distinguish between central and peripheral dopamine pathways in the mechanisms of neurodegeneration. A dissociation of putative mechanisms of respiratory and motor impairments is tackled as well. Although this purely experimental study cannot be directly extrapolated to human pathophysiology, the corollaries have been drawn concerning the potential repercussions of the respiratory and motor impairments for the physiotherapeutic procedures in the management of chronic neurodegeneration.

■ **INTRODUCTION**

Parkinsonism belongs to neurodegenerative disorders. The underlying mechanism is the progressing atrophy and degeneration of dopaminergic neurons of the brain nigro-striatal pathway and other neighboring pathways. It is estimated that 1-2% of European population over 60 years of age are affected. The disorders is manifested by motor and non-motor deficits, the latter are concerned with deficits of cognition, memory, disordered emotional state, and others.

The motor symptoms, such as akinesia, muscle rigidity, tremors, postural instability are due to degeneration of the basal mid-brain ganglia which control motor aspects. The substantia nigra, where there are dopaminergic neurons and dopamine is the most abundant neurotransmitter, constitutes an essential part of these brain structures (Hirsch et al., 1988). Dopamine is essential for both motor control and breathing regulation. In parkinsonism, dopaminergic neurons degenerate.

Breathing disorders are one of infrequently thought of impairments in parkinsonism. Disordered ventilation, however, leads to chronic hypoxia (Bouquet et al., 1999), which in turn worsens quality of life and increases general morbidity, inclusive of declined brain function and neurological motor symptoms. Studies on respiration in parkinsonism are scarce and the results are contentious. There are reports of lung ventilation impairment and a decreased ability of the respiratory system to generate stimulatory ventilatory responses (Pokorski et al., 2018; Rasche et al., 2010; Serebrovskaya et al., 1998), but also of no real change in ventilation (Seccombe et al., 2013). The mechanisms that could underlie the impairment of ventilation are unclear. These mechanisms may have to do with a deficit of central dopamine, a neurotransmitter which is essential for respiratory regulation, but they may also have to do with postural changes, rigidity of the chest muscles, generalized neuropathy, and the like. It is known that dopamine is stimulatory for ventilation at the central brain level (Huey et al., 2000), but it is inhibitory for ventilation at the peripheral level of the carotid body, the sensory paired organ that generates the stimulatory ventilatory responses to hypoxia (Ward and Bellville, 1982).

■ **OBJECTIVE AND HYPOTHESIS**

The objective of the present study was to assess the state of ventilation in parkinsonism and the ability of the respiratory system to generate the stimulatory ventilatory responses. Further, the study attempted to assess whether the eventual ventilatory impairment would specifically depend on a dopamine deficit, which would ascribe a secondary role to the impairment of the respiratory musculo-skeletal breathing pump. This objective was achieved by studying the role of dopamine in the ventilatory responses to hypoxia and behavioral changes of parkinsonism. The core of the investigation was to distinguish between central, normally stimulatory, and peripheral inhibitory carotid body-related dopaminergic effects. The role of dopamine was assessed by blocking the dopaminergic activity with domperidone, a specific peripheral antagonist of dopamine D2 receptors, and centrally by increasing dopamine availability with L-DOPA, a central dopamine precursor.

In this work we set out to get insight into the breathing regulation in the reserpine model of parkinsonism in rats. We attempted to distinguish between the role of the central and peripheral dopaminergic transmission in parkinsonism using pharmacological tools. Possible repercussions for physical and cognitive rehabilitation of dopamine insufficiency in parkinsonism are also discussed.

■ MATERIALS AND METHODS

The study was conducted in accord with the guiding principles for the Animal Care and Use of the Declaration of Helsinki of the Medical World Association. Three-month old adult Wistar rats were used in the study. The symptoms of parkinsonism were induced with reserpine, an inhibitor of synaptic monoamine transporter (2.5 mg/kg) followed by α-methyltyrosine, an inhibitor of tyrosine hydroxylase - the essential enzyme in dopamine synthesis (250 mg/kg), injected intraperitoneally. The appearance of parkinson-like symptoms was verified in behavioral tests, demonstrating the absence of locomotive activity and the lack of motivation to explore the surroundings (open field test) or to change the forcibly imposed inconvenient body position (tail suspension test).

Ventilation and its acute responses to hypoxia were recorded in a rodent plethysmograph in conscious unrestrained rats in the normal and hypoxic (8% O_2 balanced with N2) conditions, with CO2 remaining uncontrolled. The results of both functional and behavioral investigations during the full-fledged parkinsonism were referenced to the control data obtained from the same rat before the induction of parkinsonic symptoms.

Data were expressed as means ±SE of minute ventilation normalized to the kilogram of body weight. The main statistical elaboration consisted of a t-test for the comparisons of ventilation at the corresponding time points (control versus parkinsonism), one-way ANOVA for repeated measurements for the assessment of ventilation differences along the course of a 3-min hypoxia test, and two-way ANOVA with the response time and condition (control versus parkinsonism) as two-factor domains. Differences were defined as significant at a p-value of less than 0.05.

■ RESULTS AND DISCUSSION

The major finding of the study was that resting lung ventilation and its stimulatory responses to hypoxia were strongly impaired in parkinsonism. The impairment was all along the response profile, amounting to *ca* 33% in hypoxia compared to the control level. Notably, peak augmentation of ventilation during hypoxia, appearing at 30 sec from stimulus onset, was inhibited. Thus, parkinsonic symptoms evidently decreased the ability of the respiratory system to match the increased demand for oxygen. The role of peripheral dopaminergic transmission in the carotid body in parkinsonism was assessed by blockade of peripheral D2 receptors with domperidone (1 mg/kg). Domperidone increased, almost doubled, the hypoxic response in the healthy condition. In contradistinction, domperidone failed to increase ventilation in parkinsonic rats, which indicates a decrease in dopamine availability in the carotid body in the reserpine model of parkinsonism. On the other hand, L-DOPA (2 mg/kg) with benserizide (6.25 mg/kg), centrally acting precursor of dopamine, significantly increased breathing in parkinsonic rats in both resting state and along the course of the hypoxic response in contrast to the healthy condition where it failed to act that way. From these results it may be judged that the content of dopamine decreases at both central and peripheral levels in parkinsonism, but the impairment of respiration is related to the central rather than peripheral carotid body deficit in dopamine.

Concerning locomotor activity, it drastically decreased almost to null in parkinsonism. L-DOPA, central dopamine agonist, did not influence locomotor activity, although it tended to decrease the time the animal remained immobilized in the tail suspension position. This slight improvement was lackluster compared to the increase in breathing caused by L-DOPA. The dissociation of musculomotor (lack of improvement or small improvement in behavioral motor tests) and breathing (appreciable improvement in ventilation) points to the prevailing role of central dopamine insufficiency rather than a direct respiratory muscle pump weakness in the impairment of ventilation in parkinsonism. The respiratory muscle pump insufficiency is also less likely since this pump was able to drive ventilation in response to increased availability of central dopamine. This dissociation of behavioral locomotive and respiratory effects also suggests that behavioral impairment of parkinsonism depends on the neurotransmitter mechanisms other than dysfunction of the central dopamine pathway.

As above mentioned, domperidone, a peripheral dopamine antagonist, failed to increase ventilation in reserpine-induced parkinsonism as opposed to its action in the healthy condition, which suggests the exhaustion of carotid body dopamine. Domperidone also decreased locomotor activity in both healthy and parkinsonic conditions, which suggests a role of peripheral dopamine, blocked by domperidone, in counteracting motor impairment of parkinsonism. Thus, the effects of peripheral dopamine seem dichotomous. Since endogenous dopamine in the carotid body is likely inhibitory for breathing (Welsh et al., 1978), its deficit in old age could somehow facilitate breathing and counteract its impairment in parkinsonism, although respiration seems to depend mostly on the central dopaminergic drive. On the other hand, peripheral dopamine seems to have an advantageous influence in that it counteracts motor impairment in neurodegenerative conditions. It is unclear how the content of dopamine and its receptors changes in other peripheral organs, e.g., adrenal gland or kidney, changes with advancing age when parkinsonic symptoms most often develop. Nonetheless, there are natural ways of boosting both central and peripheral dopamine levels, such as balanced diet consisting of probiotics, fish oil, vegetables and minerals, almonds, and caffeine drinks. Most notably, regular exercise improves dopamine pathways, all of which may help improve motor activity and coordination as well as brain function and mental health. Summing up, resting ventilation and ventilatory responses to hypoxia are dampened in parkinsonism. The impairment of ventilation in parkinsonism has to do with the central dopamine insufficiency more than with its peripheral deficit in the carotid body. That may be judged from the stimulatory ventilatory effect on ventilation of L-DOPA, a dopamine precursor. Locomotor activity is strikingly diminished in reserpine-induced parkinsonism. This effect is not mitigated by the central action of L-DOPA. Locomotive impairment is thus mediated by mechanisms other than central dopamine insufficiency. Therefore, ventilatory and behavioral alterations in neurodegeneration are underlain by a complex interplay of divergent mechanisms that are not yet full well unraveled. These findings raise the awareness of the respiratory impairment and thus worsened oxygen supply through the lungs

and, consequently, tissue oxygenation in parkinsonism. The role of peripheral dopamine in breathing impairment is yet to be elucidated. However, peripheral dopamine seems clearly advantageous in overcoming motor disability.

The results of this experimental study cannot be directly extrapolated to human medicine and rehabilitation. The corollary, however, may be drawn that nutritional and physiotherapeutic measures are indispensable in the management of parkinson-like conditions to maintain the best possible quality of life and to slow down disease progression. The added value such measures is that it could also lead to general improvement of brain function, and thus also a drive to respiration emanating from the brainstem, thereby mitigating chronic hypoxia. Pulmonary physiotherapy, including proprioceptive neuromuscular facilitation of respiratory muscles, is essential to this end. Breathing exercises, through appropriate movements of the chest, activate muscle spindles in the inter-costal respiratory muscles, leading to a greater chest expansion, better oxygen supply, reduction of dead space ventilation, a decrease in the feeling of breath shortness, and cognition. In particular, integrated rehabilitative approach of thermal aquatic environment, combined with neuromuscular manual stimulation, to activate the natural link between sensory visceral and somatic neuronal motor pathways, appears highly recommended in neurodegenerative conditions (Barassi et al., 2020; Barassi et al., 2019; Barassi et al., 2018). Comprehensive rehabilitation program should also include nutritional and behavioral aspects.

Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publi-

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