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OLFACTORY FUNCTIONS AT THE INTERSECTION BETWEEN ENVIRONMENTAL EXPOSURE TO MANGANESE AND PARKINSONISM

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Abstract

The olfactory function can be affected by occupational and environmental exposure to various neurotoxicants that can be transported through the olfactory pathway. Olfactory impairment is a highly recurrent non-motor dysfunction in Parkinson's disease and is considered an early predictive sign of neurodegeneration. Changes in olfactory perception may be caused by a dopaminergic dysregulation, possibly related to changes at the level of dopamine receptors. Manganese is an essential element that can become neurotoxic in various conditions inducing an overload in the organism. Being actively transported through the olfactory tract, manganese can cause impairment of olfactory function and motor coordination in different age groups like children and elderly. Odor and motor changes are interrelated and may be caused by a Mn-induced dopaminergic dysregulation affecting both functions. Given these findings, further research is imperative on the possible role of manganese exposure as a pathogenetic factor for Parkinsonism.

Keywords

Olfaction; Parkinson's disease; manganese

Introduction: causes of olfactory impairment

Olfaction is a sensory function that allows identifying different substances in the environment based on their chemical-physical characteristics. Although not indispensable for humans to survive like for many animal species, it is fundamental for the perception of warning signals. Olfaction can trace subliminal stimuli that are important regulators for human behavior, for immediate decision making.

The olfactory function has been studied extensively at the cellular level only since the discovery of a variety of olfactory receptors in the early 1990s [1]. Olfactory disorders recognize several causes: mechanical [2], infective [3], traumatic [4], iatrogenic [5] [6], metabolic [6], neurologic [7]. Exposure to toxic substance such as organic solvent [8],

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metals [9], alcohol [10] can also cause olfactory impairment. The prevalence of olfactory impairments related to occupational exposure to chemicals may be ranging 0.5–5% of all olfactory dysfunctions, considering both exposure to chemicals and the use of pharmaceutical drugs. This rate may be underestimated and occupational and environmental exposure may account for a significant part of "idiopathic" smell disorders that are estimated of 10–25% of all olfactory problems within the general population. Olfactory disturbances have been reported in workers chronically exposed to cadmium, chromium, manganese, arsenic, mercury, organic lead, acrylates, styrene, and solvent mixtures. Different methods are generally adopted, with a large component of subjective evaluation that affects studies comparability [11].

Olfactory dysfunction is a frequent non-motor impairment in idiopathic Parkinson's disease [12]; recent data indicate that over 95% of the patients present significant olfactory loss [13]. Research on non-motor deficits in Parkinson's disease indicates that olfactory function may be considered as an early clinical feature of the disease, preceding motor symptoms by years [14]. Neuropathological results in post-mortem studies of Parkinsonian patients have revealed formation of Lewy Body in the olfactory bulb [15] and in other brain regions, such as the anterior olfactory nucleus, the piriform cortex, the amygdaloid complex, the entorhinal cortex and hippocampal formation [12]. Indirect evidence suggests that dysfunction of the dopaminergic pathways from mesencephalon to the piriform cortex may play a role in olfactory impairment in Parkinson's Disease [16]. Another explanation for the olfactory loss is the observation of increased dopaminergic neurons in the olfactory bulb: the increase of inhibitory dopaminergic cells may lead to pronounced hyposmia or functional anosmia [17] [18].

Transport of xenobiotics –including particles – along the olfactory nerve provides a route (nose-to-brain) for delivery to the central nervous system (CNS) that bypasses the protective blood brain barrier [19]. Manganese is transported through the olfactory tract and can, especially when carried by nanoparticles (< 0.1 μm in one dimension), reach the brain regions like the olfactory bulb, striatum, cortex and cerebellum [20].

Manganese neurotoxicity

Manganese is an essential element but can become neurotoxic when exceeding the homeostatic range in the organism. Diet is the physiological absorption route for manganese and inhalation is the typical route for occupational and environmental exposure. Once in the bloodstream, manganese is rapidly distributed to various organs and tissues including the bone and the brain. Elimination from the brain is based on a very slow efflux rate. This poses potential risk for long-term effects due to progressive accumulation and slow elimination rate. Causes of manganese overload can be due to excessive absorption through drinking water or inhalation of airborne particles from various occupations like mining, steel and ferroalloy industry, dry-alkaline production, welding, use of manganese based pesticides like maneb and mancozeb. Environmental exposure is determined by industrial emission or traffic emission from gasoline containing methyl-cyclopentadienyl manganese tricarbonyl (MMT). Neuromotor, neurosensory and cognitive effects have been observed in welders with relatively low manganese exposures [21] – [27]. These findings are similar to those observed in other Mn-exposed populations such as battery production [28] [29], ferroalloy production [30] – [32] and ore-processing [33] [34]. Early evidence of pre-clinical neuropsychological alteration include reduced performance on neuropsychological testing, poor eye-hand coordination and hand steadiness, reduced reaction time, reduced cognitive flexibility and poor postural stability [35]. Other symptoms commonly reported include headache, weakness, memory loss, sleep disturbance, irritability, anxiety disorders, and gait disturbance. These effects have been associated with Mn deposition in the brain as measured

with magnetic resonance imaging in otherwise normal industrial populations [36]. Manganese can affect also cognitive function in children, with decrements in memory, verbal learning and intelligence test [37] – [41]. Few studies of environmental Mn exposure in children focused on motor functions [42].

Manganese is mostly found in the divalent form, implicating the divalent metal transporter 1 (DMT1) as the most important transporter of this element. DMT1 is highly represented in the basal ganglia, which is a target area for both Parkinsonism and manganese toxicity [43]. DMT1 contributes to neurodegeneration in animal models [44] and certain DMT1 polymorphism have been related to Parkinson's disease [45]. At the same time, rats exposed to manganese welding fumes mimicking occupational exposure have shown increased DMT1 mRNA expression related to neurodegeneration [46]. Studies with vertebrate models like the *Caenorhabditis elegans* have further shown selective manganese induced neurodegeneration toward Dopaminergic neurons [47]. A role for DMT-1 has been observed also in enhanced manganese olfactory transport, especially in anemic animals [48]. Manganese exposure has been shown to increase the prolactin levels in rats [49] and humans including children [50], as further indication of changes in the dopaminergic system.

Odor and neuromotor assessment in Mn exposed populations

Our group has extensively studied the effect of manganese exposure from occupational and environmental exposure in the province of Brescia, Italy. In this area, ferroalloy plants have been operating for about a century until 2001 causing extensive impact of heavy metals in Valcamonica, a geographically closed environment determined by a pre-Alps valley. Follow-up of the workers has shown motor abnormalities related to blood manganese and to cumulative exposure indices calculated using the average annual exposure to airborne particles of each workers, multiplied by the number of years at the corresponding job task [30] – [33]. The dose-responses obtained in the workers dataset have been used as a basis to extrapolate protective exposure levels for the general population by Health Canada that has resulted in a reduction of the Canadian Reference Concentration for Mn from 011 to 0.05 $\mu g/m^3$ [51]. An increased prevalence of Parkinsonism has been observed among the population residing in the vicinities of these plants, with a significant correlation between the Bayesian Standardized Mortality Ration for Parkinsonism and the levels on manganese in the deposited dust [52].

Further assessment of neurobehavioral functions has been conducted with motor, cognitive, behavioral and sensory testing in population strata including adolescents and elderly residing in the historically exposed area of Valcamonica and in the reference area of Lake Garda. Individual exposure to airborne particles was assessed with 24 hour personal sampling and chemical analyses of metal concentrations in the filters. Soil metal concentrations were also assessed as a proxy of cumulative exposure from airborne emissions. Several associations were observed between Mn exposure and abnormalities of motor and olfactory functions in both age groups. Regression models showed impairment of motor coordination (Luria-Nebraska test, $p=0.0005$), hand dexterity (Aiming Pursuit test, $p= 0.0115$) and odor identification (Sniffin' task, $p=0.003$) associated with soil Mn concentrations, and tremor intensity with hair ($p=0.01$) and blood ($p=0.005$) Mn concentrations, among the adolescents of the impacted area [53]. The elderly subjects residing in the same areas showed similar impairment of motor coordination, hand dexterity and odor identification as the adolescents [54].

The influence of genetic polymorphism was assessed considering the ATP13A2 gene, also known as PARK9, for a protective role in both Parkinson's Diseases and Mn toxicity. Polymorphisms rs4920608 and rs2871776 significantly modified the effects of Mn exposure

on impaired motor coordination in elderly, also after adjustments for age and gender [54]. In addition, the rs2871776 G allele that was associated with the worst effect of Mn on motor coordination was linked to alteration of a binding site for the transcription factor Insulinoma-associated 1 (INSM1). This gene plays an important role in the developing CNS, and especially of olfactory progenitors, as shown in mouse [55] and human embryos [56].

Further assessment of the data from adolescents and elderly residing in the exposed area show that both olfaction (measured with the Sniffin' Sticks test) and motor coordination (measured with the motor subtests of the Luria-Nebraska battery) are mostly impaired among the elderly residing in the exposed area compared to the elderly living in the reference area. Olfactory and motor scores of the elderly are increasingly impaired compared to the adolescents that show the same pattern of higher deterioration in the exposed area compared to the reference one (table 1). This observation implies further deterioration of physiological ageing of these functions caused by manganese exposure. Further analysis of the inter-correlation between odor and motor scores is reported in table 2 and shows significant correlation coefficients among the elderly for motor coordination (Finger Tapping, Digit Symbol, Luria Nebraska testing), memory (Digit Span) and body sway (Sway Area, Sway Intensity, Sway velocity).

Conclusive remarks and future research

Changes in olfactory perception may be caused by a dopaminergic dysregulation, possibly related to changes at the level of dopamine receptors. Manganese is an essential element that becomes neurotoxic in various conditions inducing an overload in the organism. The toxico-kinetics of this element indicate the brain as the main target of manganese deposition and the slow elimination rate from this organ poses the precondition for possible delayed neurodegeration due to various overload conditions. Being actively transported through the olfactory tract, manganese can cause impairment of olfactory function and motor coordination. Odor and motor changes are interrelated and may be caused by a Mn-induced dopaminergic dysregulation affecting both functions.

The interconnection between manganese and dopaminergic toxicity through changes in DMT1 expression warrant further research on the possible role of manganese exposure as a pathogenetic factor for Parkinsonism. Emerging literature shows neurotoxic effects from airborne particles, especially of ultrafine dimension carried through the olfactory tract. Therefore the role of olfactory transport and brain deposition of manganese mandates further research to assess the pathogenetic mechanism of different brain functions like olfaction and motor coordination that are likely to be under control of the same dopaminergic regulation.

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Table 1

Comparison between Mn level in surface soil, airborne particles, blood, and score of odor and motor functions in adolescents and elderly residing in Valcamonica (VC) and Garda Lake (GL)

Variable	Area	Adolescents		Elderly	
		Mean	Median	Mean	Median
Air Mn (ng/m^3)	VC	49.47	31.39	26.41	18.42
	GL	27.37	24.72	20.96	17.62
P value		0,035		<0,001	
Soil Mn (ppm)	VC	958.16	897.49	1025.99	922.86
	GL	426.58	408.58	421.08	410.04
P value		<0,001		<0,0001	
Sniffin' Sticks	VC	9.61	10,00	8.60	9,00
	GL	10.08	10,00	9.30	10,00
P value		0,004		0,0213	
Luria-Nebraska	VC	62,76	61,00	52,22	53,00
	GL	67,54	66,00	56,85	56,00
P value		0,001		0,0034	

Table 2

Correlation between odor identification and neurobehavioral testing in elderly

Neurobehavioral testing	Rho	P-value
Finger Tapping - dominant hand	0,120	0,059
Digit Symbol - Raw Score	0,326	<0,0001
Digit Symbol - Correct Score	0,287	<0,001
Digit Span Forward	0,256	<0,001
Digit Span Backward	0,281	<0,001
Digit Span - Correct Total Score	0,281	<0,001
Luria-Nebraska Sum	0,180	0,0043
Luria-Nebraska Mean	0,180	0,0043
Body Sway		
Catsys - Sway Area (open eyes)	0,128	0,0528
Catsys - Sway Velocity (open eyes)	0,190	0,0039
Catsys - Sway Intensity (open eyes)	0,137	0,0373