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POSSIBLE RELATIONSHIP BETWEEN ENVIRONMENTAL POLLUTANTS/MICROPLASTICS AND SCHIZOPHRENIA ETIOLOGY AND PROGRESSION

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It is already well known that in the current environment the degree of pollution, regardless of its nature, is very high and the risk they possess over the human health is of increasing concern due to the daily exposure. One of the main environmental pollutants of modern society is plastic with all of its degradation products (especially micro- and nanoplastics) which can be easily found in everyday items from beauty products (creams, lotions, shampoos etc.) to food and even drinkable water which may have detrimental effects on individuals with pre-existing health conditions. Therefore, in the present, we want to highlight some possible effects or connections of different types of pollution with polymeric microparticles, the so-called "microplastics" in the context of schizophrenia, in order to highlight the possibility of worsening the symptoms and progression or even increasing the incidence rate of the disease due to these materials highly-present in the environment.

Keywords: microplastic, schizophrenia, pollution, risk factors.

INTRODUCTION

"Plastic materials" encompasses a plethora of widely used products categorized based on their thermoresistance from polyethylene terephthalate (PET), polypropylene (PP), polyvinyl chloride (PVC) – as the most known and used especially in constructions – to polyurethane (PUR) and resins. A vast number of studies have shown the presence of plastics smaller than 5 mm (in form of fibers, fragments, spheres) in different environments worldwide such as groundwater[1], agricultural soil[2], air[3], lakes and rivers worldwide[4–6], marine regions[7] and even in the Alpes' snow and in the Arctic region[8].

Microplastics pollution is a complex problem because of its wide-spread and its detrimental effects on health due to short or prolonged exposure are not well studies. Microplastics can be transported long distances especially in rivers and the aquatic life (fish) is prone to its ingestion leading to digestive problems before they are captured and used for human consumption[9]. Microplastics ingestion has been shown to lead to histological lesions, lethal inflammations[10] and even carcinogenic effects[11].

The presence of microplastics in different environments made human exposure to it through ingestion, inhalation and skin contact inevitable. This aspect could be connected to the higher incidence of neurodegenerative disorders, immune diseases and cancers in people[12,13]. Moreover, it has been shown in human that exposure to polystyrene particles trigger oxidative stress *in vitro* and in cellular lines studies[14]. Oxidative stress has been associated with multiple neurological disorders, such as Parkinson' Disease[15], Alzheimer' Disease[16], Schizophrenia[17] and even affective disorders such as depression and anxiety[18].

Schizophrenia is one of the most several psychiatric disorders[19]. Patients diagnosed with schizophrenia usually exhibit delusions, hallucinations, disorganized speech, severe disorganization and abnormal motor behavior. Schizophrenia is characterized by two categories of symptoms: positive and negative, complemented by cognitive deficits that lead to a functional decline over time. Negative symptoms include reduced emotional expressions, incapacity to start and carry-on tasks, alogia, anhedonia, social isolation, lack of interest, speech problems and self-neglect, while positive symptoms are much more obvious and include hallucinations, delusions and paranoia[19,20]. Schizophrenia is a disability due to the negative symptoms and recurrence is due to the positive symptoms[21]. The negative symptoms are corelated with a substantial portion of the schizophrenia associated comorbidities, but is less severe in other psychiatric disorders[20]. The first psychotic episode usually happens between the ages of 20 and 35, but with differences in prevalence between the sexes, so its incidence peaks between 20 and 25 years for men and between 25 and 30 years for women. The onset of schizophrenia can occur as early as childhood or adolescence, usually after the age of 5. Its incidence is approximately 1 in 10,000 in children and 1–2 in 1,000 in adolescents. As with early adulthood, higher rates of schizophrenia have been reported in men than in women[22].

ETHIOLOGY OF SCHIZOPHRENIA

The exact causes of schizophrenia are still unknown, but the research carried out so far in the field suggests that a combination of physical, genetic, psychological and environmental factors can cause a person to develop this condition during their lifetime[23]. Furthermore, a stressful or emotional life event could also trigger a psychotic episode[24]. Another important aspect of this pathology is that one of the most well-known risk factors is family history. In reality, however, more than 80% of people with schizophrenia, particularly psychosis, have no family history [25]. People affected by schizophrenia need permanent treatment throughout their life. The main problem in the case of this disease is the effectiveness of current treatments, currently there are no 100% effective drugs in treating the negative symptoms, namely emotional and social or cognitive disorders, which play a major role in this disease. Furthermore, even with effective drugs for positive symptoms, approximately 30% of patients develop resistance to treatment[26], and a large number of patients experience recurrence of symptoms[27].

EXPERIMENTAL MODELING OF SCHIZOPHRENIA

As in the case of other diseases or anomalies, schizophrenia is among those studied by experimental modeling using the *Danio rerio* species as a model, because an average of 83% of the modular genes involved in the elucidation of the mechanisms of schizophrenia in accordance with their important roles in the function and brain behavior are also present in the zebrafish, thus making it a good model for studying this pathology[28]. Zebrafish display a cranial architecture similar to humans. Moreover, the optic tectum, thalamus, and cerebellum of zebrafish are homologous to those present in humans[29]. Although, in the case of zebrafish, the neocortex is missing, but they are still capable of cognitive processing and complex decisions making[30]. Zebrafish exhibit a large spectrum of reactions to visual, tactile and olfactive stimuli and are capable of learning and displaying different types of memory and complex behavior such as anxiety/fear, cognition, social behavior and reward-based behavior [31].

ZEBRAFISH BEHAVIOUR AND NEUROTOXICITY

Behaviorally, several phenotypes such as fear, anxiety, aggression, learning ability, memory and circadian cycle have been modeled and characterized in zebrafish[32]. The presence of these tools, along with the sensitivity of this model to psychoactive ingredients and beyond, support its utility in various toxicity studies. In addition, zebrafish exhibit diurnal behavior, just like humans, which means that their visual acuity is well developed and simplifies observation during daytime hours. When it comes to learning and memory capacity, visual abilities are relevant in suggesting the usefulness of this model to investigate learning and memory disorders, observed in most neuropsychiatric diseases, also present in schizophrenia[33].

From another perspective, the central nervous system, but also the blood-brain barrier is particularly vulnerable and sensitive to different

chemicals, including different pollutants. Zebrafish are currently a powerful and generous toxicological model that can assess the hazards of exposure to certain chemicals and can be used to extrapolate the neurotoxic effects they have on humans. Zebrafish embryos and larvae also have convenient characteristics for chemical testing, such as small size, transparency during developmental stages, normal behavior, and standardized morphology. These qualities present the potential of this model as a good one for the identification of neurotoxicity [34].

RELATIONSHIP BETWEEN SCHIZOPHRENIA AND ENVIRONMENTAL POLLUTANTS

Regarding the implications of environmental factors, a meta-analysis carried out by Polderman and colleagues, illustrated that environmental effects constitute–up to a 55% to 66% risk for major depression, 32% for bipolar disorder and a 23% risk for schizophrenia[35]. Another study shows that low air quality (an important environmental factor) in the first years of life increases the risk of 4 psychiatric disorders including major depression, schizophrenia, personality disorder and bipolar disorder[36]. Increased knowledge of environmental risk factors and their interaction with disordered individuals is therefore vital for a more comprehensive understanding of disease causation. A study carried out in 2004, on a sample of over 7,000 people, highlighted the fact that the birth and childhood spent in the urban environment increases the chances of schizophrenia in adulthood. Thus, the risk of disease occurrence increased simultaneously with the increase in the level of air pollutants, pollution variables and traffic density, especially for benzene, carbon monoxide, their presence in the air coming from traffic [37]. Another study, much more recently, shows us that inhalable particle matter (PM_{10}), Nitrogen Dioxide and Sulfur Dioxide, are closely correlated with the onset of disease after just 4 days of chronic exposure, and the most affected are male farmers and workers aged between 20 and 50 years[38]. Heavy metals, especially from the category of xenobiotics, interfere with the neurodevelopmental system from the fetal period, increasing the chances of psychosis or schizophrenia. Thus, several studies mention metals such as lead, cadmium, and excess manganese as potential candidates for increasing the risk of developing schizophrenia[39–41].

Furthermore, the absorption capacity of heavy metals was studied, highlighting the ability of microplastics to absorb heavy metals from the environment[42,43]. These combinations of heavy metals and microplastics lead to much stronger effects, but here they can also function as "carriers", and probably long exposure could be correlated with the onset of schizophrenia, considering the effects of xenobiotics from this point of view. For example, microplastic particles have been shown to increase the body's capacity to accumulate Cadmium in zebrafish, and the effects in combination are worse compared to strict exposure to Cadmium[44].

AIRBORNE MICROPLASTICS AND THEIR TOXIC EFFECTS

Current research in the field shows us that air quality, be it indoors or outdoors, is aggravatedly decreasing with the presence of plastic microparticles worrying levels. Regarding the European countries, the study conducted by Wright *et al.*, 2020 illustrated some worrisome results in London, UK with an average of 771 MPs/m^2/day mainly constituted of polystyrene (PS), polypropylene (PP), polyethylene (PE) and fibers of acrylic materials varying in sized from 350 μm to 500 μm[45]. On the territory of Germany in 2019, an average of 275 MPs/m^2/day was recorded, predominantly fragments of PE[46], whereas in Paris, France the average particles deposited reached 110 MPs/m^2/day, mainly in the form of fibers[47]. An even more worrying outlook was reported in New Zealand with an average of 4,885 MPs/m^2/day of mainly polyethylene (PE), followed by polycarbonate (PC) and polyethylene terephthalate (PET)[48]. If we refer strictly to the indoor areas, studies showed a quantity of 6 particles/m^3 present in Portugal[49], whereas in France, the results are much more alarming revealing a deposition rate of microplastic fibers between 1586 – 11,130 fibers/day/m^2, leading to an accumulation of fibers in normally settled dust of 190–670 fibers/mg dust, of which 33% are microplastics[50].

All these particles, especially the aged ones, can absorb various pollutants from the environment, and in addition to their own intrinsic toxicity, they pose even greater risks to human health. For example, aged PE microplastics can adsorb copper and tetracycline more efficiently than new particles[51].

The accumulation in the indoor and outdoor environment determine a high possible consumption intake through inhalation is, so that an estimated amount of microplastics of (0–7.3)×104, (0–4.7)×103 and (0–3.0)×107 MPs/person/year, respectively, can even come from table salt, drinking water, and direct inhalation, respectively, according to a 2020 study[3].

The air quality is graded using the AQI index that is dependent on the inhalable particle matter, PM, which are categorized based on size A few studies to date, support the idea that poor air quality may influences the debut of the psychotic episode therefore the onset of schizophrenia. Due to these findings, researchers are pushing the recommendation to revise the European Legislation regarding air quality in order to include microplastics to the "PM" category due to their concerning toxicity, size and presence in the air especially as the World Organization of Health (WHO) has already published a detailed report on the effects of microplastics in drinking water[52]. Based on their size, microplastics could be identified as PM_{10}, due to dimensions below 10 μm, and nanoplastics as $PM_{2.5}$, due to dimensions below 2.5 μm[53].

The presence of these material in the human body is no longer surprising due to their strong present in the environment as well as their high storage properties. Thus, a recent study found microplastic particles in 13 of the 22 human lungs studied following their autopsy, with size smaller than 5.5 μm, and fibers varying between 8.12 and 16.8 μm, mainly polyethylene (PE) and polypropylene (PP) materials[54]. Moreover, another study presented an even more worrying fact, microplastic particles with sizes between 5 and 10 μm detected in 6 maternal placentas, in a number of 12 polymeric particles, especially polypropylene (PP)[55].

These studies only further illustrate that people are highly exposed to these materials, whether through the air or through ingestion. Toxicity studies of these polymeric materials based on their composition show different toxicity also when tested on human cell cultures.

A recent *in vitro* study on human brain cell lines showed a possible correlation between the exposure to Polystyrene (PS) to the oxidative stress response in a cause-effect relationship, modulated by ROS overproduction and microplastic accumulation[14]. Another study carried out on human cells, using Polypropylene (PP) particles (~ 20 μm and 25–200 μm), this time, demonstrated that direct contact with these particles and cells may have the potential to cause harmful effects, in addition to ROS overproduction, by inducing cytokine production in immune cells, rather than direct cell toxicity, in a size- and concentration-dependent manner[56]. Another material tested, also on human cell cultures, namely polyethylene (PE), showed cytotoxic capacity by affecting intestinal and lung epithelia viability but also inducing a pro-inflammatory response in them[57].

CONCLUSIONS

In conclusion, all this information indicates that we are prone to the microplastics accumulation, inhalation and ingestion of polymeric materials that have proven toxic effects in the case of human cell cultures and zebrafish models, regardless of the environment in which we are.

Thus, a question mark is raised if for healthy people these materials present toxicity, if there is a certain pathology of a neuropsychiatric nature, then what would be the possible toxicological effects in this case considering the absorption capacity of many pollutants on the surface of these microplastics and their influence on air quality.

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