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Environmental pollution and risk of psychotic disorders: A review of the science to date

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ABSTRACT

Environmental pollution is a global problem with diverse and substantial public health implications. Although many environmental (i.e., non-genetic) risk factors for schizophrenia and other psychotic disorders have been identified, there has been comparatively little research on pollution as a possible risk factor. This is despite the fact that gene-by-environment interactions and epigenetic mechanisms are now recognized as likely facets of the etiology of schizophrenia, and the fact that pollution could potentially mediate the association between urban birth/upbringing and elevated risk. We conducted a review of the literature to date in order to summarize and synthesize work in this area. We identified 13 research reports and 16 review articles. Based on the extant knowledge in this area and what is known about the pathophysiology of schizophrenia, it is feasible that exposure to xenobiotic heavy metals such as lead and cadmium, constituents of air pollution such as particulate matter and nitrogen and sulfur oxides, organic solvents, and other constituents of environmental pollution could be component causes. Further research—from the cellular to epidemiological levels—is clearly needed. If causation is proven, enhancements of policy intended to reduce human exposure to environmental pollution could reduce the burden of schizophrenia and possibly other mental illnesses.

1. Introduction

Environmental pollution is a subject of increasing worldwide public health concern. According to the World Health Organization (WHO, 2014), in 2012 approximately 7 million premature deaths were attributable to air pollution exposure, confirming that air pollution is presently the world's major environmental risk for health, having an impact on several diseases (e.g., coronary artery disease, cerebrovascular accidents, obstructive lung disease, lung carcinoma, and acute lower respiratory infections in childhood). Ambient particulate matter (PM) pollution was the ninth principal risk factor in 2010 with regard to the global burden of disease (Lim et al., 2012). Air pollution commonly takes origin from combustion of fossil fuels, as well as industrial and agricultural processes. Air pollutants of main public health interest involve PM (e.g., organic and elemental carbon, metals [e.g., lead], and polycyclic aromatic hydrocarbons), carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (Suades-González et al., 2015). Associations between air pollutants and central nervous system (CNS) diseases have being shown (Block et al., 2012).

Risk for psychosis is linked to both genetic and environmental factors, with increasing evidence that the environment can largely influence genetic effects (e.g., through gene-by-environment interactions and epigenetic mechanisms) and vice versa (van Os and Sham, 2003). Interestingly, both past and current studies show that urbanicity of birthplace and upbringing is related to a higher incidence of schizophrenia and other non-affective psychoses (Heinz et al., 2013). Air pollution could conceivably be one of the candidate factors to explain this association. Yet, relatively little attention has been given to the question of the role of pollution as a risk factor for psychosis. The aim of our work is to briefly review all of the studies (including both review articles and original research) in which the relationship between pollution and psychotic illness was examined.

2. Methods

We searched the Pubmed electronic database for all articles up to February 19, 2016. Search terms included “schizophrenia” or “psychosis” or “psychoses” or “psychotic” or “schizophreniform” or “schizoaffective” or “delusional” or “catatonia” combined with “pollution” or “pollutants” or “polluting” or “particulate” or “smog.” The

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search included all languages. 98 articles were identified. We selected 29 studies related to pollution's effects on human subjects: 13 were research reports, and 16 were review articles. We excluded 69 articles, on the basis of the following exclusion criteria: a) studies unrelated to the topic, b) studies related to pollution's effects on animals, c) studies on cigarette smoke or on passive tobacco smoke, and d) letters or general comment papers not reporting research findings.

3. Results

Main findings from the research reports are presented in Table 1, in descending chronological order, and also described narratively below. Main conclusions from the review articles are briefly summarized narratively below.

3.1. Review articles

Thirteen of the 16 review articles (Brown Dzubow et al., 2010; Cirla and Gilioli, 1978; Guilarte et al., 2012; Holden, 1995; Kelly et al., 2010; Marchetti, 2014; McGrath and Scott, 2006; Mena, 1974; Mortensen, 2001; Opler and Susser, 2005; Orisakwe, 2014; Padhy et al., 2014; Terry et al., 2011) explicitly refer to a possible association between environmental pollution and an increased risk of schizophrenia/psychosis; the other three review articles are less specific, relating to a possible role of environmental pollution in increasing the risk of mental disorders (Landrigan, 1983; Lederbogen et al., 2013), or of emotional and behavioral dysfunctions (Dumont, 1989). Among all environmental pollutants, lead (Pb), a xenobiotic heavy metal, is certainly the most mentioned potential candidate linked to an increased risk of schizophrenia/psychosis ($n = 7$ dedicated review articles) (Guilarte et al., 2012; Landrigan, 1983; Marchetti, 2014; Mortensen, 2001; Opler and Susser, 2005; Orisakwe, 2014; Terry et al., 2011). A xenobiotic substance is an element or chemical compound foreign to a particular organism or biological system; a xenobiotic is not normally endogenously produced by or expected to be found within that organism or biological system. The second most mentioned candidate is air pollution ($n = 5$ dedicated review articles) (Kelly et al., 2010; McGrath and Scott, 2006; Mortensen, 2001; Padhy et al., 2014; Terry et al., 2011), a more general term used to describe the introduction of particulates, biological molecules, or other harmful substances into earth's atmosphere that can have adverse effects on humans and the ecosystem. The third most mentioned pollutant that may play a role in schizophrenia is cadmium (Cd), a xenobiotic heavy metal similar to Pb ($n = 2$ dedicated review articles) (Marchetti, 2014; Orisakwe, 2014).

3.2. Research reports

All 13 research reports describe a possible connection between environmental pollution and an increased risk of schizophrenia/psychosis. Most of the studied pollutants belong to the group of air pollutants ($n = 11$ research reports) (Bowler et al., 1991; Kelly et al., 2010; Kiselev et al., 1997; Lary et al., 2015; Lundberg et al., 2009; Pedersen et al., 2004; Perrin et al., 2007; Sanders, 1964; Tong et al., 2016; Vaneckova and Bambrick, 2013; Yackerson et al., 2014). Among air pollutants, particulates, referred to as particulate matter or PM (i.e., microscopic matter suspended in the earth's atmosphere), appear to play an influential role recently (Lary et al., 2015; Tong et al., 2016; Vaneckova and Bambrick, 2013; Yackerson et al., 2014). Also, oxides of nitrogen (NO_x), particularly NO_2 (Pedersen et al., 2004; Tong et al., 2016), and organic solvents (Bowler et al., 1991) like tetrachloroethylene, also known under the name perchloroethylene (Perc or PCE) (Perrin et al., 2007), seem to have a significant role. We found only one research report related to risk of schizophrenia induced by PCE-contaminated water (Aschengrau et al., 2012), and one research report in which the risk of schizophrenia was related to reactive oxygen species whose generation can be induced by exposure to different environmental pollutants (Korotkova et al., 2011). A complete list of pollutants identified in the 13 research reports (and their role for an increased risk of schizophrenia/psychosis) is presented in Table 1.

4. Discussion

Schizophrenia is a complex, debilitating, and clinically heterogeneous neurodevelopmental syndrome, associated with variable functional impairments in social, emotional, perceptual, and cognitive domains (Green and Glausier, 2016; Mittal et al., 2016; Owen et al., 2016;). To date, no single factor has been found to characterize all patients with schizophrenia; this holds for potential etiological factors, as well as clinical manifestations. Patients with schizophrenia differ in clinical presentations and features, developmental and family backgrounds, cognitive functioning, and even neuropathology and neurochemical processes (Mittal et al., 2016). The etiologies of schizophrenia are indeed multifactorial, with different patients probably having very different constellations of "component causes," or risk factors, both genetic and environmental (Green and Glausier, 2016; Owen et al., 2016; Sawa and Snyder, 2002). Multiple developmental pathways eventually lead to disease onset and both genetic and environmental factors are sources of constitutional vulnerability, having implications for prenatal and postnatal brain development (Mittal et al., 2016). Therefore, the complex clinical features of schizophrenia are underpinned by an equally complex pathogenesis, in which a likely genetic susceptibility confers a vulnerability to a number of environmental menaces, especially during particular developmental periods (Green and Glausier, 2016).

A number of "environmental" risk factors, both biological and psychosocial, have been identified (Owen et al., 2016) in addition to genetic risk factors that still remain poorly understood. A role of epigenetic processes is suggested by the fact that data on consistently replicated genetic effects are absent, and by the evidence for stable modifications in gene expression after certain environmental hazards (Cariaga-Martinez et al., 2016). Several environmental risk factors, affecting early neurodevelopment or having an effect at later timepoints, contribute to schizophrenia (Owen et al., 2016). Those observed most commonly and frequently include obstetric complications, maternal illnesses during pregnancy (above all infections such as maternal influenza), early-life CNS infections, and nutritional deficiencies. Additionally, negative family emotional environment and childhood maltreatment, adolescent cannabis use, socioeconomic factors, immigration, and urbanicity (being born or raised in cities), have been commonly described as risk factors for schizophrenia (Green and Glausier, 2016; Laurens et al., 2015; Owen et al., 2016).

Urbanicity, specifically urban birth and upbringing, is a well-defined risk factor for schizophrenia; in this field, hypothesized mediators like neighborhood fragmentation, low social cohesion and social capital, and the psychological stress of urban life, have been singled out (Green and Glausier, 2016; Haddad et al., 2015; Heinz et al., 2013; Krabbendam and van Os, 2005; Laurens et al., 2015; Owen et al., 2016; Torrey and Bowler, 1990). Urbanicity could also potentially be related, at least in part, to environmental pollution (Heinz et al., 2013; Kelly et al., 2010; Lundberg et al., 2009; McGrath and Scott, 2006; Mortensen, 2001), which has been largely neglected compared to some of the other non-genetic environmental risk factors.

The findings from our review show that both recent and less recent studies link environmental pollution and especially air pollution exposure, to an increased risk of schizophrenia or psychosis. There are feasible biological mechanisms by which some of the specific pollutants could affect brain development in a way that could increase risk for schizophrenia. Epidemiological and observational studies have shown that air pollution has well-defined adverse effects on the respiratory and cardiovascular systems (Genc et al., 2012), and recently emerging data from both human and animal studies suggest that certain CNS diseases, such as Alzheimer's and Parkinson's diseases, cerebrovascular insults, and neurodevelopmental disorders, may be related to air pollutant

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