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Review article

Carbon monoxide pollution and neurodevelopment: A public health concern

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ABSTRACT

Although an association between air pollution and adverse systemic health effects has been known for years, the effect of pollutants on neurodevelopment has been underappreciated. Recent evidence suggests a possible link between air pollution and neurocognitive impairment and behavioral disorders in children, however, the exact nature of this relationship remains poorly understood. Infants and children are uniquely vulnerable due to the potential for exposure in both the fetal and postnatal environments during critical periods in development. Carbon monoxide (CO), a common component of indoor and outdoor air pollution, can cross the placenta to gain access to the fetal circulation and the developing brain. Thus, CO is of particular interest as a known neurotoxin and a potential public health threat. Here we review overt CO toxicity and the policies regulating CO exposure, detail the evidence suggesting a potential link between CO-associated ambient air pollution, tobacco smoke, and learning and behavioral abnormalities in children, describe the effects of subclinical CO exposure on the brain during development, and provide mechanistic insight into a potential connection between CO exposure and neurodevelopmental outcome. CO can disrupt a number of critical processes in the developing brain, providing a better understanding of how this specific neurotoxin may impair neurodevelopment. However, further investigation is needed to better define the effects of perinatal CO exposure on the immature brain. Current policies regarding CO standards were established based on evidence of cardiovascular risk in adults with pre-existing comorbidities. Thus, recent and emerging data highlighted in this review regarding CO exposure in the fetus and developing child may be important to consider when the standards and guidelines are evaluated and revised in the future.

Contents

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1. Introduction

For over fifty years, air pollution has been suspected as an underlying cause of a wide variety of disease processes (Mustafic et al., 2012). Although commonly encountered indoor and outdoor environmental pollutants have been linked with a range of pulmonary, cardiovascular, and immune system maladies, evidence has only recently emerged to suggest a relationship between air pollution and neurodevelopmental impairment (Block et al., 2012; Mustafic et al., 2012; Wang and Pinkerton, 2007). It is now believed that indoor and outdoor air pollution may be associated with certain neurocognitive abnormalities and behavioral disorders including the autism spectrum (Block et al., 2012; Vrijheid et al., 2012). Infants and children appear to be uniquely vulnerable to the neurotoxicity of air pollution due to the susceptibility of the brain during critical periods in development and the potential for exposure to such neurotoxins in both the fetal milieu and the postnatal environment (Grandjean and Landrigan, 2006).

Air pollution is a heterogeneous mixture of gases and particulate matter (Mustafic et al., 2012). The main gaseous components of air pollution are ozone, carbon monoxide (CO), nitrogen dioxide, and sulfur dioxide (Mustafic et al., 2012). As a by-product of incomplete combustion of hydrocarbons, CO is a major component of motor vehicle-related pollution, tobacco smoke, and gas stove pollution (US Environmental Protection Agency, 2012; Vrijheid et al., 2012). Therefore, CO is a common contaminant of both indoor and outdoor environments. Because it can cross the placenta to gain access to the fetal circulation and the developing brain, CO is of particular interest as a neurotoxin and a public health threat (Greingor et al., 2001; McGregor et al., 1998). Here we review overt CO toxicity and the policies regulating CO exposure, detail the evidence suggesting a potential link between CO-associated ambient air pollution, tobacco smoke, and learning and behavioral abnormalities in children, describe the effects of subclinical CO exposure on the brain during development, and provide mechanistic insight into a potential connection between CO exposure and neurodevelopmental outcome.

2. Environmental CO and overt toxicity

2.1. CO poisoning

CO is a colorless and odorless gas that can be poisonous to humans (Iqbal et al., 2012a; Kao and Nañagas, 2005). It is generated by incomplete combustion of carbonaceous fuels such as oil, gasoline, coal, wood, and tobacco (Bauer and Pannen, 2009; Kao and Nañagas, 2005). Because CO is non-irritating and imperceptible in the air we breathe, exposure is often not recognized and acute CO toxicity is commonly underappreciated and misdiagnosed (Kao and Nañagas, 2005; Iqbal et al., 2012a). CO continues to be the leading cause of poison-related mortality in the United States (Kao and Nañagas, 2005; Iqbal et al., 2012a). Unintentional, non-fire-related CO exposure leads to greater than 20,000 emergency room admissions, more than 2000 hospitalizations, and up to 6000 deaths each year (Centers for Disease Control and Prevention, 2007, 2008; Iqbal et al., 2012b; Kao and Nañagas, 2005).

2.2. Sources of environmental CO

Vehicle exhaust contributes to 75% of all CO emissions in the US and up to 95% of all emissions in US cities (US Environmental Protection Agency, 2012). The remainder is due to steam boilers, industrial processes, solid waste disposal, and miscellaneous other sources (Raub, 1999). Indoor CO sources include tobacco smoke (from cigarettes, cigars, as well as water pipes or hookahs), gas cooking ranges, combustion space and water heaters, coal or wood burning stoves, and improper use of generators and charcoal grills (Daher et al., 2010; Iqbal et al., 2012a; Raub, 1999). Although CO exposure occurs year-round, poisonings peak in the winter months due to the increased use of heating devices in closed spaces (Kao and Nañagas, 2005; Iqbal et al., 2012a).

Global background CO concentrations average between 50 and 120 parts per billion (ppb) in the troposphere and approximately 60% of these levels have been attributed to human activity (Raub, 1999). Although short-term peaks occur each day and demonstrate seasonal variability, CO levels are greatest in the northern hemisphere and over the last decade annual outdoor urban levels in the US have averaged between 2 and 5 parts per million (ppm) (Raub, 1999; US Environmental Protection Agency, 2012). Vehicle exhaust contains up to 100,000 ppm CO and levels can reach between 10 and 12 ppm within passenger compartments of automobiles during heavy traffic (Raub et al., 2000; US Environmental Protection Agency, 2012). Even higher concentrations are encountered in semi-closed environments routinely exposed to vehicle exhaust such as parking garages, tunnels, and indoor ice skating rinks (Pelham et al., 2002; US Environmental Protection Agency, 2012). CO toxicity has been reported in children riding in the back of pick-up trucks and exposure commonly occurs with certain recreational activities such as boating (Hampson and Norkool, 1992). Indoor levels can rise to 100 ppm with use of gas stoves and CO levels can range between 5 and 35 ppm within smoking rooms based on the number of lit cigarettes and the size of the room (Kao and Nañagas, 2005; Gül et al., 2011; Jo et al., 2004). Thus, infants and children can be exposed to CO in a variety of commonly encountered environments.

Water pipe (hookah) tobacco smoke deserves special mention. This is because the incidence of hookah smoking has increased dramatically around the world over the last few years (Eissenberg and Shihadeh, 2009; Martinasek et al., 2014). Sidestream hookah smoke contains 30 times the amount of CO as a single cigarette and CO levels within the ambient environment of hookah bars can be as high as 50 ppm (Daher et al., 2010; Zhou et al., 2014). In addition, several cases of acute symptomatic CO poisoning have been reported in teenagers and young adults following water pipe use (La Fauci et al., 2012; Misek and Patte, 2014; von Rappard et al., 2014). CO toxicity in these cases manifested with syncope or loss of consciousness (La Fauci et al., 2012; Misek and Patte, 2014; von Rappard et al., 2014). Thus, hookah use is rapidly becoming a public health issue and combustion of water pipe tobacco is a significant source of indoor CO pollution in certain environments.

2.3. Mechanisms of overt CO toxicity

When inspired, environmental CO diffuses rapidly across the alveolar capillary membrane and binds to hemoglobin, forming