Air pollution may affect the function of central nervous system and cause related diseases

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Abstract: After understanding human's health problem is related with the air pollutant, some research shows that different air pollutant which was caused by different ways are related with different illness. However, with different air pollutant, they have similar ways to invade human's body and their brain. Some scientific data also shows the difference of human's brain after they are exposed with air pollutant. Therefore, it's important to understand the response and behavior of the human's brain after they get attacked from those air pollutant. With the human's brain's response, it's helpful for us to keep studying the mechanism that describes the process of how those pollutant hurt the brain. Some research can help us determine the basic procedure. With the exposure of air pollutant, they can change the gene's expression. What's more the evidence from other studies can help suppose the truth that air pollutant can also leads to some disorders, such as Parkinson's disease and Alzheimer's disease. After that, the relationship between Alzheimer's disease and air pollutant is also important for us to understand, some data from the research helps understand more details about different air pollutant's toxicity, with those information we can understand more detailed information about the pollutants and their relationship with disease.

1. Introduction

Air pollution (AP) could be described as the mixtures of chemicals and biological material in the ambient air, which can have adverse effects on humans and other living organisms. Nowadays, with industry development all over the world, AP has become one of the most severe problems. Particular matters, traffic related particles, heavy metal particles, and other types of pollutants may be inhaled, and some of them will enter the brain. Millions of people worldwide are chronically suffering from APs. In some areas, highly concentrated air pollutants are extremely detrimental to life. According to the World Health Organization (WHO) the number of deaths caused by AP reached 7 million annually. In that case, to research how these pollutants damage our brain is quite necessary for this could tell us how to protect us from those pollutants and finally release the reflection of these air pollutants.

Air pollutants may affect the central nervous system (CNS) through a variety of molecular pathways. Among those pathways, systematic inflammatory response has become significant in cities that are constantly exposed to AP. Long-term exposure to APs may contribute to a change in gene expression which can be considered as the pathological evidence. The inflammation of neuron will trigger the production of inflammatory cytokines, which will damage the CNS through the blood circulation. Recently, evidence from epidemiological and experimental studies shows that APs are strongly related to certain neurological disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD). The incidence and death caused by such diseases have been increasing rapidly since the last decades. This is probably associated with the lower air quality condition in some areas of the world.

In this paper, we will discuss potential ways of how air pollutants invade our brain and the reflection of different regions of the brain. Detailed harm of air pollutants to the CNS and the molecular

mechanism will be provided. Furthermore, some related neurological diseases, especially AD, will be particularly investigated in terms of relationships.

2. Air Pollutant can invade human's mind

2.1. Toxic part in air pollution

As for the air pollutant, it could be produced by the factory, the car's emissions or fossil fuels that are not completely burned. However, the air pollutant is toxic because they contain some elements which are toxic to human's body. As for evidence, the coke oven emissions would produce the pollutants such as benzene, toluene and xylene, which have already been determined carcinogenicity after they are breathed into human's body [1]. Besides, the major air pollutants that were produced during the coke-making process could be concluded as Total Suspended Particulate, $PM_{3.5}$, PAHs and Benzene [1]. Except for factory produce, exhaust gas from automobile emissions also accounts for a large part of air pollutants. For cars that use diesel as fuel, those diesels' compounds such as unburned hydrocarbons, hydrocarbons and carbon monoxide are all toxic for human's body [2]. Moreover, some citizens' behavior can also cause toxic AP. For example, based on research, burning daily life's trash can release some toxic metals such as arsenic (As), cadmium (Cd), copper (Cu) and zinc (Zn) [3]. Those metal create chronic poisoning, which cause skin lesions, nervous system, digestive and cardiovascular system disorders, and has cumulative toxic effects after human breath those pollution in. Besides burning straw, which is a way that farmers used to deal with the wheat field, can create some compounds particles, which is toxic after human breath them in. Toxic particles, such as acetylsyringone, fluoranthene and organochlorine pesticides, can be absorbed by human and hurt humans' health through breath [4].

2.2. Process of air pollutant's invade

After those pollutants are produced, spread into the air and breath into human's brain, it's also important to understand how those pollutants spread out in human's body. Some research thinks except the pass-way that pollutants could choose to undergo from nose to lungs and finally come into different place, it's possible for some tiny pollutants to pass the skull and hurt human's brain directly [5].

In the Table 1, it's easy to find difference between the normal brain and brain that may be hurt by pollutants. Some researchers think air pollutants such as $PM_{2.5}$ can invade human's respiratory system from their nose. After invading the nose, those pollutants can stimulate the process of creating pro-inflammatory cytokines. The next step is $PM_{2.5}$ can access into olfactory bulb and then they got chance to get into digestive system and respiratory system. After passing though those system, $PM_{2.5}$ can cause some reactive oxygen species, which break the barrier of brain and caused some different disease [6].

Table.1. The Median Power Frequency Data of Central Location Before and After Exposure in 3 Min each [5]

	MPF at FpI (Hz)				MPF at C3 (HZ)			
	Sham		Diesel		Sham		Diesel	
	pre	post	pre	post	pre	post	pre	post
1	5.7	7.6	6.4	8.0	6.5	8.7	6.9	9.4
2	7.1	8.3	8.7	12.6	7.8	6.1	9.5	11.2
3	7.8	8.5	7.4	8.4	9.7	8.4	6.7	10.2
4	8.3	7.7	8.7	9	11.5	9.9	9	9.6
5	9.2	9.1	9.8	8.4	10.5	12.3	9.7	9.2
6	7.1	10.7	8.9	11	11	11	9.0	11.9
7	15.3	12.7	9.3	14.4	15.1	13.6	7.9	9.1
8	10.2	11	7.4	11.3	7.6	9.1	8.3	9.3
9	7.5	7.3	6.6	7.1	7	6.3	7.2	8.0
10	6.7	7	8.9	11.2	11.2	12.3	7.4	9.1
Mean	8.5	9.0	8.2	10.1	9.9	9.8	8.2	9.7
SD	2.7	1.9	1.2	2.3	2.6	2.6	1.1	1.1

2.3. Different parts of brain's response to air pollutants

After checking the pollutant's spread, it's easier to show how does the brain's different parts response to those pollutant as they invade. In the research, the rat's brain was divided into six main parts to check their own response: hippocampus, frontal cortex, cerebellum, olfactory bulb, tubercles and striatum and the final research shows the levels of pro-inflammatory cytokines tumor necrosis factor alpha and interleukin-1 alpha raised up in striatum part, besides in the case that cerebellum gets the lowest active, OB+T shows the highest level in those parts of brain [7]. Except for that, some research also shows the pollutant such as 13C can raise cerebellum's level of δ-13C values [8]. In this case it's possible to believe that the air pollutant could transport into human's mind and successfully hurt human's mind or raise the level of some values.

By concluding those evidence, we can assume that different air pollutant can be breath by human and hurt human's mind though respiratory system and nerve system. However, it's not enough to only understand the process of air pollutants' invaded, the function of how those process happened is also important.

3. The Molecular Mechanism of Air Pollution on The Nervous System

After those air pollutants intrude into our brain, they will cause pathological changes at the molecular level of the brain in a variety of forms. In this paper, the abnormal gene expression of neurons and inflammatory response caused by long-term exposure to air pollutants will be discussed as the main molecular mechanism.

3.1. Air pollution may cause abnormal expression of gene

Studies have shown that long-term exposure to NO_2 inhalation at low concentration will cause damage to the brain and abnormality of mitochondria [9]. The specific molecular process is that NO_2 causes changes in hemorheology of normal rats and eventually leads to pathological damage of cerebral cortex. The expression of endothelial contractile factor ET-1 and eNOS gene was changed, and the expression of stimulating factors such as TNF-α, ii-β and ICAM-1 was up-regulated, which induced apoptosis [9]. In this process, abnormal ultrastructure of mitochondria leads to the change of its vitality and damage of function. Microarray hybridization revealed that long-term NO_2 exposure induced a more than two-fold and statistically significant change in the expression of 552 genes, including synaptic composition and function, external stimulus response and cell cycle regulation, which may ultimately contribute to neurodegenerative diseases and cancer [9]. For instance, Gene expression could affect the AD development [10]. Carriers of APOE4 allele could have a higher risk of developing AD when they live in an area with high AD [11].

Experimental studies have shown that tiny particles of polluted air could cause cell cycle arrest, cell apoptosis and inhibition of neuronal cell proliferation in different ways, and these effects are caused by oxidative stress-mediated abnormal DNA hydroxymethylation [12]; The levels of inflammatory factors, nitrocellin and microglia markers in the brain tissue of rats were significantly increased after the inhalation of diesel engine exhaust gas, indicating that polluted air can cause a variety of neuroinflammatory responses and abnormal gene expression [13]. Hence, AP may adversely affect CNS in numerous different ways, resulting in many illnesses like AD, PD which may be affected by age, genetics and regional differences of humans. Molecular mechanism mainly includes inflammation.

3.2. Specific mechanisms of systemic inflammation

1) Production and action pathway of cytokines: Systemic inflammation results in the production of cytokines such as interleukin-1 β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-A (TNF-A), which act on and adversely affect neurons in the brain through the blood circulation. Systemic inflammatory response could be connected to the CNS through various pathways [14].

The first involves areas of the brain that lack a complete blood-brain barrier (BBB) [15]. In these areas, cytokines diffuse freely from the blood into the brain parenchyma and can interact with macrophage populations. The second major pathway crosses the intact BBB: cytokines activate endothelial cells, which signal perivascular macrophages, which in turn communicate with resident macrophages in the brain parenchyma [16]. A third pathway involves sensory afferent to the vagus nerve, which, after Inflammation is induced in the peritoneal cavity, communicates with a population of neurons in the brain stem [16]. The fourth pathway is the direct active transport of cytokines across the BBB, and studies have shown that this process may affect cognitive function [16].

It can thus be seen that a key component of the signaling process from the blood to the brain involves the activation of macrophage populations within the CNS. These macrophage populations can synthesize inflammatory mediators, which in turn induce the secretion of other signalling molecules (such as prostaglandins) to signal neurons, leading to neurological diseases.

2) Inflammation and neurodengenerative diseases: Constant inflammation could result in partial histopathology, which means the long-term inflammatory stimuli or maladjustment of the body's normal processing mechanisms. Constant stimulation can be caused by environmental factors or the formation of endogenous factors (such as aggregates of proteins) that the immune system perceives as signals of "strange substances". The inflammatory response that establishes a feed-forward loop may exceed the normal regulatory range of the body. Uncontrolled inflammation can increase the production of neurotoxic factors of the underlying disease state, and inflammation is associated with many neurodegenerative diseases, including AD, PD, amyotrophic lateral sclerosis (ALS), and multiple sclerosis [16].

Recent studies have shown that inflammatory response has become an important process of nerve injuries induced by a variety of environmental pollutants. People living in areas with severe AP have increased inflammatory responses in tissues such as the lungs and brain [17, 18]. Long-term exposure

to $PM_{2.5}$ has been shown to trigger brain inflammation and aggravate neurodegenerative diseases [19]. Upregulation of signal-dependent transcription factors NFKB and AP1, thereby inducing the increased release of pro-inflammatory cytokines TNF-A and 1L-1β, may be one of the mechanisms of Inflammation induced by $PM_{2.5}$ exposure [20].

4. Connection of Air Pollution and Alzhermer's Disease

4.1. Background information on Alzheimer's disease

AD, a disease that can cause degeneration of the brain and lead to brain atrophy, is one of the most common causes of dementia [21-23], which is the main type of dementia for elderly over 65 and is accounting for two-thirds of all dementia cases [24]. According to the Centers for Disease Control and Prevention, the number of deaths caused by AD was increased about 71% between 2000 and 2013 [25]. This data indicates that we may not pay enough for such a dangerous disease.

4.2. Air pollution may lead to the Alzheimer's disease

Recently, evidence showed that AP might have adverse effects on the CNS and contribute to the development of CNS diseases [26-27]. Some of the pollutants are related to AD. Onset symptoms of AD were seen in humans, and animals exposed to AP [28]. Jung et al. conducted a 9-year cohort follow-up study of 95690 individuals (aged>65 years) in Taiwan and found that the risk of AD prevalence increased 211% with each increase in O_3 concentration of 10.91 PPB. Each 4.34 μg/m 'increase in $PM_{2.5}$ concentration increases the risk of AD by 138%, suggesting that long-term exposure to O_3 and $PM_{2.5}$ higher than EPA standard is significantly correlated with the increased risk of AD [29]. Till now, we are still poorly understood the AD and the mechanism of neurotoxicity of AP. However, evidence of connection between AD and AP was detected by many researchers.

Early study through the autopsy of dogs and people in Southwest Metropolitan Mexico City where the concentration of AP is significant found AP can damage many parts of CNS (e.g., BBB, olfactory bulb). AP may contribute to the decreasing of cognitive function for both human and dogs [30]. Some association of Alzheimer's type pathology and respiratory tract inflammation in dogs was detected [31]. Later in 2004, [32] observed that people who are exposed to severe AP might have brain inflammation and accumulation of 42 amino acid forms of β-amyloid, two causes of the neuronal dysfunction, indicating the AD could be induced by AP.

Other than autopsy studies, vivo and vitro tests of rats and mice were carried out to evaluate the toxicity of different kinds of AP [26].

Most air pollutants (e.g., particulate matters, ozone, residual oil fly ash) have neurotoxicity through different mechanisms and routes (e.g., loss of DA neuron, increase tumor necrosis factor alpha and decrease mentor activity). The neurotoxicity of air pollutants can be varied in a wide range, but the overall adverse effect on CNS is similar, through oxidative stress, DNA damage, microglial activation, neuroinflammation, and so on [33].

4.3. Air pollution may relate to a decrease in the average score of cognitive tests

In the research of the elderly, by doubling the traffic-related particle black carbon for long-term exposure, the average score of a battery of seven cognitive tests for 680 men from the U.S was decreased [33]. The results suggested that traffic-related AP may have adverse effects on older men. Similarly, in another research, people who are younger and age around 20 -59 showed the same pattern as older people, which is that increase in AD may decrease cognitive function. Thus, other evidence shows that AD may impact cognitive ability, which may relate to AD development.

5. Conclusion

AP is threatening in our regular life. Nowadays, lots of people in different places are suffering from excessive and chronic AP. The negative effects it had brought is a global issue for public health. Air pollutants especially for fine particulate matter and other tiny molecules that may invade into our

brains, are contributing to the development of several CNS diseases and cognitive diseases such as AD and PD. However, even many studies have been carried to determine the adverse effects of AP. The damage on CNS is widely neglected. As far as human know how harmful these APs are, we can encourage more and more cities to carry out air purification process to improve the sanitation. Besides, different air pollutants will cause response of different regions of our brain, which is important for us to understand the mechanism of AP in the CNS. While we know why and how some air pollutants work, we may find ways to prevent infecting with CNS diseases and to detoxify these pollutants. Solving air quality related diseases can save thousands of people's live in the future. To achieve this goal, more extensive and intensive collaborations should be carried to investigate the exact mechanism, and related information of its danger should be advertised to raise people's awareness.

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