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<원저>

Changes in Brain Activity of Rats due to Exposure to Fine Dust Using ^{18}F-FDG PET

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^{18}F-FDG PET를 이용한 미세먼지 노출에 따른 쥐(rat)의 뇌 활성도 변화

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Abstract Fine dust threatens human health in various forms, depending on the particle size, such as by causing respiratory, cardiovascular, and brain diseases, after entering the body via the lungs. The aim of this study was to correlate fine dust exposure with changes in brain blood flow in Sprague Dawley rats by using micro-positron emission tomography and elucidate the possibility of developing cerebrovascular diseases caused by fine dust. The subjects were exposured to an average fine dust (particulate matter 2.5) of 206.2 ± 7.74 to ten rats four times a day, twice a day for 90 min. Before the experiment, they were maintained at NPO to the maximize the intake of ^{18}F-fluorodeoxy glucose(^{18}F-FDG) and minimize changes in the ^{18}F-FDG biomass depending on the ambient environment and body temperature of the rats. PET images were acquired in the list mode 40 min after injecting ^{18}F-FDG 44.4 MBq into the rats tail vein using a micro-PET scanner pre and post exposure to fine dust. We found that the whole brain level of ^{18}F-FDG standardized uptake value in rats averaged 5.21 ± 0.52 g/mL pre and 4.22 ± 0.48 g/mL post exposure to fine dust, resulting in a statistically significant difference. Fine dust was able to alter brain activity after entering the body via the lungs in various forms depending on the particle size.

Key Words : Dust, Standard uptake value (SUV), Micro-PET scanner, Rats, ^{18}F-fluorodeoxy glucose(^{18}F-FDG), Exposure conditions
중심 단어 : 표준섭취계수(SUV), Micro PET 스케너, 쥐, ^{18}F-fluorodeoxy glucose, 노출조건

Ⅰ. Introduction

Recently, particulate matter(PM) has been a major cause of environmental contamination due to carbon dioxide emissions from fossil-fuel combustion, exhaust gas from automobiles, dust from power generation facilities, etc. Ultra-fine dust of size under 2.5 μm contains heavy metals(copper, lead, zinc, chromium, and cadmium) depending on the source of the agent and may affect people's health depending on their level of exposure to harmful substances, such as nitrates, sulfates, etc[1,2]. Fine dust enters the human body in the respiratory system, causes lung disease after depositing in the pulmonary alveolus, and increases the

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risk of cardiovascular diseases, such as angina and myocardial infarction, by increasing the viscosity of blood[3,4].

In addition, fine dust entering the respiratory system breaches the blood-brain barrier (BBB) from inflammatory response. Most previous studies to date have focused on the effect of PM on the respiratory system. No study has investigated the effect on cerebrovascular or brain function of fine dust. The aim of this study was to correlate PM exposure with changes in brain blood flow in Sprague Dawley(SD) rats using micro positron emission tomography(micro-PET) and elucidate the possibility of developing cerebrovascular diseases.

II. Material and Methods

1. Experimental design

We used a exposure and generation box of fine dust comprising a transparent acrylic box(400(W) × 300(D) × 300(H) mm) and plastic box(200(W) × 200(D) × 200(H) mm).

Only fine dust was introduced through the exposure box with PM10(diameter less than 10 ㎛) through the filter.

We performed the brain PET scan using a Focus 120 micro-PET system(Concorde Microsystems Inc., Knoxvill, TN)(Fig. 1).

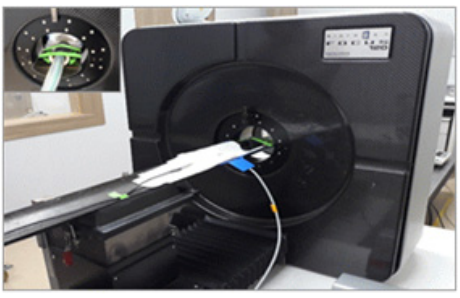

Fig. 1. Micro PET scanner

We measured fine dust using the Light Scattering Fine Dust Meter(JSMY-1000, 3M corporation). We used a generation and exposure box of fine dust comprising a transparent acrylic box and plastic box. Only fine dust was introduced through the exposure box with PM10 (diameter less than 10 ㎛) through the filter (Fig. 2).

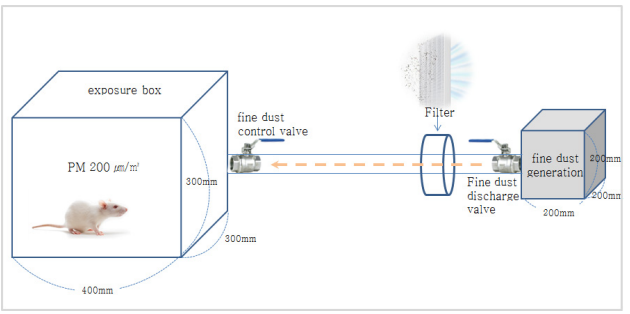

Fig. 2. Fine dust generation and exposure box

We performed the brain PET scan using a Focus 120 micro-PET system. We measured fine dust using the Light Scattering Fine Dust Meter. We used a generation and exposure box of fine dust comprising a transparent acrylic box. Only fine dust was introduced through the exposure box with PM10 through the filter(Fig. 2). We performed the brain PET scan using a Focus 120 micro-PET system. We measured fine dust using the Light Scattering Fine Dust Meter.

2. Animal or Experiment animal

A total of ten 6-week-old SD rats were divided into a 12-h night/day (lighting at 8:00 am) cycle for 1 week. Rats were adapted to the experimental environment by allowing them to freely consume food and water at 21℃ ± 1℃ temperature and 60% ± 10% humidity.

To maximize the ingestion of ^{18}F-FDG, rats used in the experiment were provided with only water and maintained at an empty stomach for 18 h. The temperature was maintained at 29°C ± 2℃ and humidity at 60% ± 10% in a quiet and dark environment to minimize changes in the biodistribution of ^{18}F-FDG depending on the surrounding environment and temperature.

3. ^{18}F-FDG Micro-PET imaging

An ^{18}F-FDG dose of 44.4 MBq was injected into the tail vein[5]. Rats underwent ^{18}F-FDG uptake at room temperature and humidity for 30 min. After ^{18}F-FDG

uptake, the inhalational anesthetic Isoflurane was administered, and rats were positioned on a PET table. The anesthetic concentration was maintained at 2% during imaging. We used a Focus 120 micro-PET system with high resolution(0.5~1.0 mm) for small animals and acquired images in the list mode for 30 min after an interval of 40 minutes following the ^{18}F-FDG injection. Attenuation of the skull bones of rats was speculated to be small during image acquisition. The image was reconstructed using the ordered subset expectation maximization(OSEM) algorithm with 12 repetitions of the subset and 18 map iterations without attenuation correction. To reduce the glucose consumption of rats before imaging, their body temperature was maintained at 36℃ ± 1℃ using a heating pad composed of carbon installed on the inspection table. First, basal scintigraphy was performed on each rat before exposure to fine dust. After exposure to fine dust four times for a total of 6 h, images were acquired in the same manner as in base photography.

4. Quantitative image analysis & Statistical analysis

The experimental results were analyzed using PMOD 3.2v(PMOD Technologies Ltd., Zurich, Switzerland) to measure the standard uptake values of ^{18}F-FDG PET images reconstructed with the OSEM algorithm to quantify the standard uptake values of the entire rat brain area.

Statistical analysis was performed using Kolmogorov-Smirnova and Shapiro-Wilk test with the SPSS statistical program(ver. 14) to test the parametric method with a small sample size with all ten rats participating in the experiment. Normal distribution was confirmed with p〈0.200* and p〈0.241. The paired t-test was performed to correlate changes in brain blood flow before and after exposure to fine dust in mice. A p-value 〈0.05 was considered to be statistically significant.

Ⅲ. Results

1. Concentration of fine dust

The average concentration of fine dust exposed to a total of ten rats was 399.8 ± 10.02 ㎍/㎥ at PM10, 206.2 ± 7.74 ㎍/㎥ at PM2.5, and 169.7 ± 7.06 ㎍/㎥ at PM1.0(Table 1).

Table 1. The fine dust exposure concentration (unit : ㎍/㎥)

No	day	PM	PM 10			PM 2.5			PM 1.0		
			0 min	45 min	90 min	0 min	45 min	90 min	0 min	45 min	90 min
1	1	am	398	399	401	217	208	211	180	175	173
		pm	382	386	389	208	201	211	177	168	165
	3	am	399	390	398	206	209	213	170	166	159
		pm	387	400	403	210	216	210	169	170	166
2	1	am	399	402	400	210	217	234	166	185	157
		pm	400	389	399	202	211	206	172	180	154
	3	am	397	401	402	203	209	213	180	174	179
		pm	399	408	403	211	209	200	165	172	180
3	1	am	402	399	389	210	203	201	155	177	169
		pm	398	380	388	195	195	189	168	167	170
	3	am	390	381	376	203	199	190	170	164	160
		pm	376	388	384	203	200	206	177	165	158
4	1	am	408	411	398	206	201	213	181	177	154
		pm	403	416	399	201	199	203	177	178	175
	3	am	399	410	402	211	218	201	180	167	158
		pm	402	388	400	199	204	215	181	175	169

No	day	PM	PM 10			PM 2.5			PM 1.0		
			0 min	45 min	90 min	0 min	45 min	90 min	0 min	45 min	90 min
5	1	am	403	410	385	200	213	198	169	155	167
		pm	422	401	406	210	192	208	173	166	159
	3	am	399	385	395	211	208	201	169	167	173
		pm	402	411	413	203	204	230	169	177	175
6	1	am	400	413	433	210	199	190	159	160	171
		pm	410	402	416	213	192	213	181	166	170
	3	am	398	402	399	209	216	200	177	168	164
		pm	406	418	402	216	215	208	180	174	160
7	1	am	405	400	398	201	198	196	158	161	160
		pm	389	402	388	203	210	199	166	177	165
	3	am	398	399	403	209	211	194	169	168	170
		pm	403	400	398	199	195	203	168	171	167
8	1	am	412	399	385	213	200	201	155	177	180
		pm	413	408	401	214	210	200	169	170	174
	3	am	388	403	389	208	231	213	181	173	173
		pm	400	408	403	207	201	206	170	169	177
9	1	am	389	388	398	213	218	203	165	170	169
		pm	413	418	406	197	201	211	170	174	181
	3	am	403	420	412	213	210	206	167	174	168
		pm	398	394	392	220	216	209	182	172	170
10	1	am	388	390	401	211	210	201	166	159	172
		pm	403	431	413	211	206	199	172	169	166
	3	am	400	388	393	203	205	201	180	176	170
		pm	394	406	401	199	194	201	154	160	162
total	Averege ±SD		399.4 ±8.7	401.1 ±11.4	399.0 ±10.0	207.2 ±5.8	206.4 ±8.3	205.2 ±9.1	170.9 ±7.7	170.3 ±6.3	167.7 ±7.2

2. Changes in brain activity before and after exposure to fine dust

Brain PET was performed 40 min after the ^{18}F-FDG injection to determine changes in brain activity pre and post exposure to fine dust, and the following results were obtained.

After the ^{18}F-FDG injection pre and post exposure to fine dust, the average standard intake coefficient for each major part of the rat brain ranged from 5.76 ± 0.90 to 4.78 ± 0.52 g/mL in the cerebral frontal lobe area, 4.71 ± 0.49 to 3.66 ± 0.48 g/mL in the lower area (hippocampus), 5.38 ± 0.59 to 4.10 ± 0.47 g/mL in the midbrain area, and 4.77 ± 0.58 to 3.55±0.46

Table 2. Partial Brain ^{18}F-FDG uptake by pre and post exposure to fine dust (unit : g/ml)

Resion	pre exposure	post exposure
Motor cortex	5.76 ± 0.90	4.78 ± 0.52
Striatum	5.89 ± 0.83	4.79 ± 0.50
Hippocamus	4.71 ± 0.49	3.66 ± 0.48
Midbrain	5.38 ± 0.59	4.10 ± 0.47
Thalamus	5.82 ± 0.80	4.68 ± 0.48
Cerebellum	4.77 ± 0.58	3.55 ± 0.46

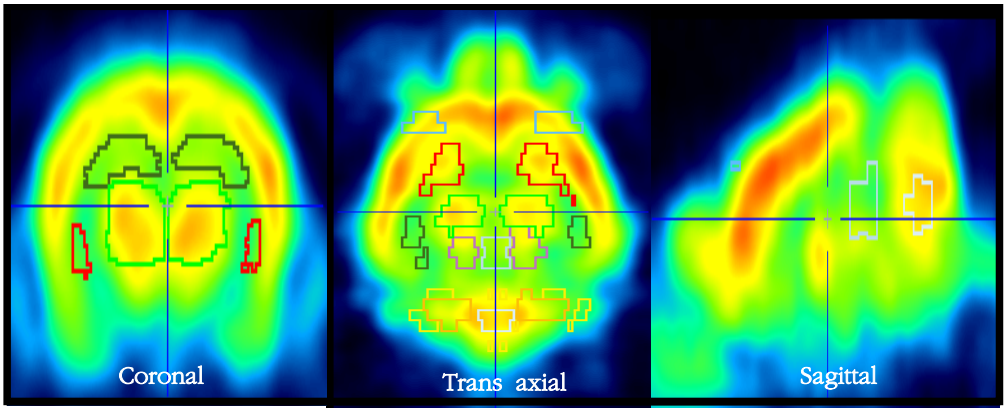

Fig. 3. The partial brain imaging regions ROI of Rat

Table 3. Whole brain ^{18}F-FDG uptake by pre and post exposure to fine dust (unit : g/ml)

No	pre exposure	post exposure	*p*-value
1	4.03	3.42	p<0.000
2	5.64	3.37	
3	5.80	4.23	
4	5.10	4.19	
5	5.67	4.52	
6	4.96	4.64	
7	5.32	4.86	
8	5.58	4.38	
9	4.91	4.22	
10	5.12	4.40	
Average ± SD	5.21 ± 0.52	4.22 ± 0.48	

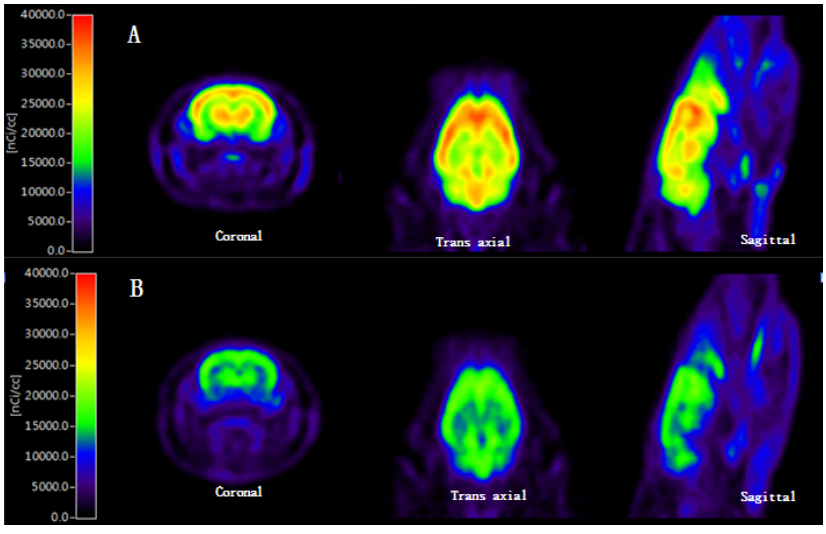

Fig. 4. The whole brain imaging pre(A) and post(B) exposure to fine dust in Rat

g/mL in the cerebellum area(Table 2, Fig. 3).

The ^{18}F-FDG standard intake coefficient for the whole brain was 5.21 ± 0.52 g/mL before exposure to fine dust and decreased to 4.22 ± 0.48 g/mL after exposure, indicating a statistically significant difference (Table 3, Fig. 4).

Ⅳ. Discussion

Recently, public interest in fine dust has been increasing, and attention is being paid to the causal relationship between fine dust and disease emergence.

Fine dust of various sizes(PM10 = less than 10 μm; PM2.5 = less than 2.5 μm; PM1.0 = less than 1.0 μm) is generated from the exhaust of automobiles, chimneys of factories or thermal power plants, and construction sites. Most fine dust is artificially generated by humans[6,7].

The effect of the generated fine dust on the human body is already well-known through many several studies[8-10]. In 2013, the World Health Organization (WHO) International Cancer Institute designated it as a group 1 carcinogen because air pollutants and fine dust are associated with a high incidence of cancers, including lung cancer[11]. Fine dust mainly flows through the respiratory system and enters blood vessels, which can worsen symptoms of cardiovascular disease or cause a stroke. The Korea Centers for Disease Control and Prevention and Miller KA et al. reported that long-term exposure to fine dust increases the mortality rate according to the concentration of fine dust entering the body. According to previous studies, when the concentration of fine dust(PM10) increases by 10 $\mu m/m^3$, the mortality rate of cerebrovascular disease increases by 10%, and when the concentration of fine dust (PM2.5) increases by 10 $\mu m/m^3$, the risk of death from cerebrovascular disease increases. It was found to have increased by 80% and increased by more than 20% because of stroke[12].

In particular, An experimental study on the capillaries of mice and reported that fine dust induces cytokines and reactive oxygen species, decreasing the expression of tight junction proteins in cerebral blood flow barrier from alteration of the signal of the membrane transporter, thereby altering its function. Fine dust introduced into the systemic circulation through the respiratory tract may eventually enter the brain through the cerebral blood flow barrier[5].

Therefore, the aim of this study was to investigate the changes in the activation of the mouse brain according to short-term exposure to fine dust. As a result, ^{18}F-FDG intake of the entire brain was 5.21 g/mL on average pre exposure but decreased to an average of 4.22 g/mL post exposure. There was a significant difference, indicating an effect of fine dust on brain activation($p<0.05$; Tables 1 and 2). Human brain cells are closely linked to the glucose metabolism process that supplies energy; therefore[13], changes in glucose and oxygen metabolisms in a physiological environment are accompanied by changes in blood flow in the brain, unless there is a pathological abnormality in the blood vessels of the brain. Therefore, brain PET can quantitatively evaluate changes related to brain structure and dysfunction by imaging the brain's perfusion status, glucose metabolism, and physiological substance intake[14].

Jung et al. reported that ^{18}F-FDG, a glucose analogue, is fixed in the form of FDG-6-phosphate by glucose metabolism when injected into the body and is ingested into the brain tissue, which can reflect changes in glucose metabolism in the brain. Changes in brain activity can be observed based on changes in glucose metabolism[15].

According to the results of the overall brain activity of rats, a significant decrease from 5.21 ± 0.52 before to 4.22 ± 1.48 after exposure to fine dust was confirmed(Fig. 4). As such, ultra-fine dust(PM2.5), which has a small particle size compared to other types of fine dust, is the main cause of various diseases, such as changes in the cardiovascular system and brain activity, depending on blood circulation through the alveola, as well as respiratory diseases. Undertaking countermeasures is urgent because it causes extreme stress and depression in modern society.

In our study, exposure to fine dust affected brain activity. Our limitations are that since the brain activity was evaluated after exposure to fine dust over a relatively short period of time, the effect of long-term accumulated fine dust exposure was not considered, and various concentration changes were not evaluated because the average fine dust(PM2.5) concentration was limited to 206.2 ± 7.74 μm/m3. In modern society, which has been exposed to air

pollution for a long period of time, research on the relevance of each disease is continuously being conducted. Therefore, it is necessary to study brain diseases caused by exposure to ultra-fine dust for a long time[16].

V. Conclusions

Recently, fine dust, which threatens health, has a significant impact on human health in various forms depending on the size of particles, from respiratory diseases through the lungs to cardiovascular diseases to brain diseases.

Until now, there have been reports that fine dust affects stroke and brain nervous system, but there have been difficulties in clinical application due to few previous studies. However, through this study, it was possible to confirm the correlation between fine dust and brain activity through the lungs.

Therefore, since modern society has a population distribution with weak immunity as it ages, the occurrence of fine dust should be lowered as much as possible, and various clinical studies of brain diseases caused by exposure to fine dust should be preceded.

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