Biomedical Journal of Indonesia
Journal Homepage: https://bji-fk.ejournal.unsri.ac.id

Side Stream Cigarette Smoke and Its Role in Inducing Oxidative Stress in Rat Cerebral Tissue

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ARTICLE INFO

Keywords:
Smoking
Side stream smoke
Malondialdehyde
Oxidative stress
Brain

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/BJI.v11i2.253

Received 14 March 2025;
Accepted 8 April 2025

ABSTRACT

Introduction. Smoking behavior can affect not only the individual smoker but also those around them. Individuals exposed to secondhand smoke are at risk of developing similar health problems as those faced by individuals who actively smoke. Secondhand smoke causes an imbalance of systemic oxidants and antioxidants characterized by the presence of a lipid peroxidation product, namely Malondialdehyde (MDA). The main objective of this study was to assess how exposure to sidestream cigarette smoke affects MDA levels in rat cerebral tissue **Methods.** A true experimental study was conducted using 30 male Wistar rats with a post-test only control group design. All rats were randomly divided into 5 groups, namely 1 control group and 4 treatment groups. A total of 270 cigarettes were used as exposure sources. A spectrophotometer at a wavelength (λmax) of 533 nm was used to measure MDA levels. The MDA level data were then analyzed. ANOVA and Kruskall Wallis tests were performed after evaluating the results of the Normality and Homogeneity tests. A p value <0.05 indicates significant data**. Results.** The results indicate that the group exposed to cigarette smoke using 4 cigarettes for 30 days (P4) exhibited elevated MDA levels compared to the control group. Statistical analysis showed a significant correlation between secondhand smoke and increased MDA levels ($p < 0.05$). **Conclusion.** This study results suggest that exposure to SSCS contributes to increased MDA levels in the brain tissue of Wistar rats, which indicates oxidative stress.

1. Introduction

Smoking is an example of an unhealthy lifestyle that has the potential to cause various long-term health problems and reduce the quality of life of smokers.[1] The findings of studies conducted several years ago showed that this smoking habit has the potential to increase the risk of cardiovascular disease, respiratory system disorders, stroke and cancer, as well as increasing the potential for infectious diseases.[2–5] Although included in the preventable risk factors, the development of the number of smokers, especially in Indonesia, does not show a downward trend. Statistical data shows that the prevalence of smokers aged over 15 years in Indonesia has always been above 28% since 2015,[6] and the latest statistical data in 2022 shows the prevalence of smokers aged over 15 years in Indonesia is 36.7%.[7]

The negative impacts of smoking are not only felt by the smoker himself, but also by the people around the smoker, also known as passive smokers.[8,9] The term passive smoker refers to people around active smokers who accidentally inhale cigarette smoke containing various mixtures of dangerous chemicals.[10] Cigarette smoke is divided into two categories, namely mainstream smoke or smoke inhaled by smokers and sidestream smoke or secondhand smoke, namely smoke that continues to come out of cigarette butts.[11] This makes passive smokers have the same potential for health problems as active smokers.[12,13] The negative effects of both types of cigarette smoke on the human body have been studied intensively in recent decades. Study by Shick and Glantz explained that exposure to sidestream smoke contains higher concentrations of toxic substances than mainstream smoke. They added that exposure to sidestream smoke results in increased levels of carboxyhaemoglobin, nicotine and

cotinine.[14] Then in 2014, Behera and his colleagues conducted a study that tested 4 cigarette brands and the findings showed the same opinion as Shick and Glantz, namely that sidestream cigarette smoke has higher levels of toxic substances than mainstream smoke.[15]

Exposure to side stream cigarette smoke specifically not only affects the human respiratory system, several other organs are also affected. One of the organs of the body that is susceptible to the negative effects of cigarette smoke besides the lungs is the brain.[1] This impact has been well studied and one of them is shown in an epidemiological study by Bai et al. (2020) in elderly women in China showing that exposure to secondhand smoke is associated with the incidence of decreased cognitive function, visuospatial ability, and episodic memory function.[16] Wan et al. (2024) added in their study that individuals who live in the same environment as smokers have a high risk of developing dementia.[17] Some of these findings on the impact of exposure to sidestream cigarette smoke have been previously identified. Raber et al. (2023) explained that exposure to cigarette smoke can cause oxidative stress which leads to brain injury. This has an impact on the acceleration of brain aging, especially in the hippocampus.[18] Morphological research also proves a decrease in the thickness of the gray matter of the brain tissue of mice exposed to cigarette smoke.[19]

Cigarette smoke contains thousands of chemical compounds including free radicals and oxidants in high concentrations that trigger oxidative stress. Free radicals originating from Reactive Oxygen Species (ROS) formed from cigarette smoke can cause damage to nuclear DNA and damage to cell membranes due to lipid peroxidation.[20] The cerebrum is vulnerable to oxidative stress due to free radicals due to several factors such as a very high dependence on oxygen, neuronal membranes rich in polyunsaturated fatty acids (PUFA), suboptimal antioxidant defenses, ROS-forming microglia, and non-replicable neuronal cells.[21]

Oxidative stress due to cigarette smoke exposure has been a concern in various experimental studies. A study conducted by Hendriati and Syaquie (2023) showed an increase in MDA levels which play a role in triggering the inflammatory process in the lacrimal gland tissue after being exposed for 21 days.[22] In a different case, exposure to cigarette smoke produced from electronic cigarettes also showed an increase in MDA levels.[23] This confirms that cigarette smoke sources, both from conventional and electronic cigarettes, have the same potential to increase oxidative stress, thereby contributing to various health disorders related to inflammation and cellular dysfunction.

Previous research has extensively examined the effects of cigarette smoke on oxidative stress, particularly in peripheral organs such as the lungs and liver. However, studies specifically investigating the impact of side-stream cigarette smoke (SSCS) on oxidative stress in cerebral tissue remain limited. Most prior studies have focused on mainstream smoke exposure, despite evidence suggesting that SSCS contains higher concentrations of toxic compounds due to its unfiltered nature. The purpose of this study was to prove that exposure to secondhand smoke can trigger oxidative stress in brain tissue. Oxidative stress was assessed by looking at MDA levels. Through the results of this study, it can contribute to strengthening opinions about the dangers of cigarette smoke for health, and as material for health workers to provide advice and maintain a smoke-free hospital environment. The results of this study can also encourage the birth of laws or regional regulations that can protect passive smokers.

2. Methods

This study is a true experimental study with male Wistar rats as experimental animals. The research design used post-test only control group design. This design has five groups, each of which is randomly selected. All treatments given to mice were thoroughly evaluated and received ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Hang Tuah, Surabaya (No: E/015/UHT.KEPK.03/II/ 2020).

Thirty male Wistar rats (*Rattus norvegicus*) meeting the body weight requirement of 200-250 grams and aged between 2 to 3 months were selected for the study. Through a random process, these rats were then allocated into five distinct groups for the experimental procedures with each group comprising 6 rats. These groups included 1 control group and 4 treatment groups. The treatment group consisted of Group P1 (2 cigarettes per day for 15 days); P2 (2 cigarettes per day for 30 days); P3 (4 cigarettes per day for 15 days); P4 (4 cigarettes per day for 30 days). A plastic enclosure with dimensions of 50 x 40 x 20 cm was specifically designed and set up as a designated area intended for the housing and containment of rats, providing them with a secure and controlled environment conducive to their well-being and experimental conditions. Before the initiation of treatment, a period of acclimatization will be implemented for all mice in the laboratory. Additionally, all mice will be provided with food and water ad libitum.

The setup used to expose mice to sidestream smoke consists of a ventilator, a smoke generator, and a chamber connected via silicone tubing punctuated by Heimlich valves to avoid smoke regression. The ventilator is set to provide air. The smoke-generating chamber consists of an acrylic cylinder then smoke is delivered to the acrylic chamber (length, 80 cm; width, 20 cm; height, 25 cm).[24] Each group will be put into an exposure cage. Cigarette smoke came from "Penamas" brand clove cigarettes (composition 32 mg tar and 2 mg nicotine). Smoke from cigarettes was administered into the smoking pump according to the

dose and duration in each treatment group. Cigarette smoke exposure was performed daily for 15 and 30 days.

The scalp of rats was dissected in the caudo-rostral direction at the sagittal suture line, then the cranium was cut on the side starting from the foramen magnum, and the brain tissue was removed from the meningen and cranial nervi and cut at the mesencephalon. The entire cerebral tissue was placed in an Eppendorf tube to be examined for MDA levels. A homogenate of the brain tissue was prepared and 1 ml of cold 0.9% NaCl was added, homogenized, and centrifuged at 8000 rpm for 20 min to obtain the supernatant. The supernatant was taken as much as 100 µl and put into a small test tube and added successively 550 µl distilled water, 100 µl trichloroacetic acid (TCA), and then homogenized. Into the next mixture added 250 µl HCl and 100 µl Na-thiobarbiturate and further homogenized. After the mixture is homogeneous, it is then centrifuged at 500 rpm for 10 minutes until the supernatant is obtained. The supernatant obtained was then incubated in a water bath at 100 ° C for 30 minutes. The result obtained was then centrifuged at 500 rpm for 10 minutes until the supernatant was obtained. The supernatant obtained was then measured for absorbance with a UV-VIS spectrophotometer (Hitachi U-2810 Model:122-000 No: 1819-011a, Japan) at a wavelength (λ_{max}) of 533 nm.

Quantitative data were recorded and entered into tables using the Microsoft Excel program and analyzed using the SPSS ver. 24. The collected data will be tested for normality with the Shapiro-Wilk Test, then continued with the Levene Test homogeneity test. If the data is normally distributed and homogeneous, analyze it with a parametric One-Way ANOVA test. If the data is not normal and or not homogeneous, it includes nonparametric data so that the Kruskall-Wallis Test analysis is used. Then the LSD post hoc test is carried out if there is significant data. A p-value of < 0.05 was declared significant data.

3. Results

Observations on MDA levels of each group of rats were measured on 31th day. Through the analysis, we found that the P4 group, or the group that was exposed to the smoke of 4 cigarettes/day for 30 days showed higher MDA levels than the other groups (2400.67 ± 123.90). The lowest MDA levels were found in the control group (2026.33 ± 269.98) and group P1 which was exposed to 2 cigarettes per day for 15 days (2071.83 ± 118.21). The complete results of the observation of MDA levels of each rat sample can be seen in Table 1. Through the Levene test, we found that the data were not normally distributed, so we conducted a non-parametric analysis using the Kruskal-Wallis test. The results of the analysis showed a significant relationship.

Based on the findings using the Kruskal-Wallis test, the data analysis of MDA levels was continued by performing the Mann Whitney-U test. The test results (see table 1) showed a significant relationship between the control group and the exposed group (P3 and P4) (p < 0.05), while the other groups showed insignificant results.

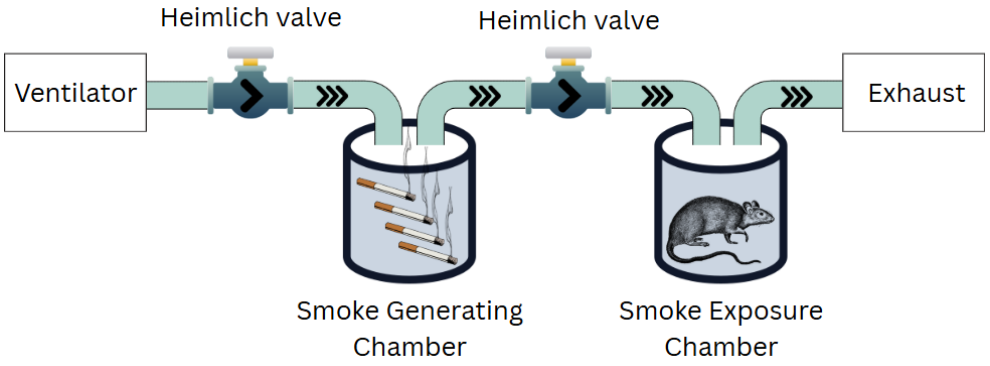

Figure 1. Treatment cage and side stream cigarette smoke exposure mechanism

Table 1. Summary of observations of MDA levels in each rat sample and the average per group, as well as the results of the Kruskal-Wallis analysis test.

Group	Exposure Doses	Duration of Exposure	Mean ± SD	Kruskal-Wallis Test
K	Without Exposure	Without Exposure	2026.33 ± 269.98*	
P1	2 cigarettes/day	15 days	2071.83 ± 118.21	
P2	2 cigarettes/day	30 days	2383.83 ± 116.70	0.01
P3	4 cigarettes/day	15 days	2400.67 ± 123.90*	
P4	4 cigarettes/day	30 days	2439.00 ± 385.27*	

*Statistically significant (Mann Whitney-U test)

4. Discussion

Unlike mainstream smoke, which partially passes through filters, sidestream cigarette smoke (SSCS) is released directly from burning cigarettes into the surrounding air. Although often overlooked, SSCS contains higher concentrations of toxic chemicals and poses serious health risks not only to active smokers but also to those exposed to secondhand smoke (passive smokers). A series of studies have shown that cigarette smoke can contain more than 4000 chemical compounds, which include not only free radicals and oxidants but also a myriad of other substances that contribute to its complex composition and potentially harmful effects on human health.[25] Valavanidis and colleagues explained in their study that cigarette smoke contains ROS in high concentrations due to the tar and nicotine content in cigarettes.[26]

The research conducted by Caliri elucidates that, in conjunction with ROS, cigarette smoke is also comprised of Reactive Nitrogen Species (RNS) compounds, each of which possesses the capability to instigate cellular damage via oxidative stress.[27] The existence of nicotine, recognized as one of the constituents present in tobacco, significantly contributes to the processes that initiate the generation of ROS within biological systems.[28] This reactive species possesses the capacity to initiate a succession of oxidative reactions within the cellular environment, thereby resulting in molecular impairment and the perturbation of cellular functionality.[29] The elaborate interplay between ROS, RNS, and nicotine highlights the intricate character of the biochemical mechanisms implicated in oxidative stress induced by tobacco smoke.[30]

The impact of cigarette smoke needs special attention because it can cause oxidative stress, which is allegedly an early sign of several serious health conditions.[31–34] Increased oxidative stress in body tissues can be influenced by how much cigarette consumption or exposure to cigarette smoke is received over a period of time.[35,36] The brain is one example of an organ in the body that is susceptible to oxidative stress.[37] The onset of oxidative stress within the cerebral region will result in impairments in memory and cognitive functions as a consequence of neuronal damage.[38]

The results of this study showed that the group exposed to cigarette smoke (4 cigarettes) experienced a significant increase in MDA levels in brain tissue in 2 different exposure duration scenarios. This finding indicates that exposure to sidestream smoke can increase MDA levels which leads to oxidative stress in rat brain tissue. These findings are in line with the study of Valenti et al. who reported an increase in oxidative stress in the brainstem area of rats exposed to sidestream cigarette smoke for 3 weeks with exposure duration of 5 times per week for 180 minutes.[39] Another study conducted by Maestra et al. on the brain tissue of rats exposed to cigarette smoke for 4 weeks with an exposure of 1 hour per day, obtained results in the form of an increase in brain tissue lipid peroxidase and significant neuronal cell apoptosis.[20] Another study also proved an increase in oxidative stress in the brain tissue of male rats exposed to cigarette smoke for 6 weeks with a duration of 2 times a day.[40]

The opposite results were shown in the group exposed to cigarette smoke from 2 cigarettes, where the results did not show any significant increase in MDA levels. This suggests that lower-dose exposure may not have been sufficient to induce excessive oxidative stress. We suspect that the dose and duration of cigarette smoke exposure are closely related to this result. Hu et al. (2014), in their study, demonstrated that rats exposed to cigarette smoke twice daily for 14 consecutive days exhibited an increase in malondialdehyde (MDA) levels and a decrease in serum superoxide dismutase (SOD) activity. These findings suggest a decline in aerobic capacity, making the rats more susceptible to fatigue.[41]

Despite the findings, we found that this study still has several limitations. First, the exposure duration and dose scenarios used in this study still do not replicate real-world exposure scenarios, such as variations in smoke concentration and exposure patterns of cigarette smoke. Furthermore, this study only focused on oxidative stress markers, without assessing potential neurobehavioral or cognitive impairments in the experimental animals. Furthermore, we only assessed one oxidative stress marker while other indicators of oxidative stress, such as protein oxidation and mitochondrial dysfunction were not analyzed in this study. Finally, in this study, we only focused on the impact of cigarette smoke exposure without exploring the protective mechanisms or relevant therapies to mitigate the effects of oxidative stress caused by cigarette smoke. Future research should address these limitations by incorporating longitudinal studies, additional biomarkers, behavioral assessments, and intervention strategies to better understand the full impact of SSCS on brain health.

5. Conclusion

Through the findings of this study, we found a significant relationship between exposure to secondhand smoke and increased levels of MDA, which indicates oxidative stress in the cerebral tissue of male Wistar rats. We also concluded that passive smokers have the same health risks as active smokers. The duration of exposure to cigarette smoke will determine how severe the negative impact is on the human body. The revelations presented in the findings possess the potential to encourage and motivate policymakers to consider the necessity of implementing even stricter and more comprehensive regulations concerning the allowances and provisions

related to smoking activities that take place in open environments as well as in various public spaces, thereby ensuring the promotion of public health and the well-being of the community at large.

6. Author Contribution

I.F. and A.R. conceived the original idea. W.E.R and M.S.R. handle data analysis. A.R wrote the manuscript with support from W.D.M.R.B.. A.R, I.F., and I.R.F collected the MDA data sample. I.F and W.E.R. supervised the project.

7. Acknowledgements

The author expresses gratitude to Universitas Nahdlatul Ulama Surabaya for the support that made this research possible.

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