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Comparison of electronic cigarette smoke and conventional cigarette smoke exposure on brain histopathology and brain-derived neurotrophic factor level

Comparación de la exposición al humo de cigarrillos electrónicos y al humo de cigarrillos convencionales en la histopatología cerebral y en los niveles del factor neurotrófico derivado del cerebro

Andhira Prabawati[1a], Aryadi Arsyad[1b], Arif Santoso[1c], Irawaty Djaharuddin[1d], Husni Cangara[2e], Nurul Hidayah[3f], Masyita Nurul Jihad[3g]

SUMMARY

Objectives: *This study aims to evaluate and compare the effects of exposure to electronic and conventional cigarette smoke on the levels of Brain-Derived Neurotrophic Factor (BDNF) and the histopathological features of the brain in rats.* **Methods**: *24 male Wistar rats were divided into three groups: a control group (no exposure to cigarette smoke) and two experimental groups exposed to either regular cigarette smoke (1.8 mg nicotine, 32 mg tar, 25 minutes/day for 4 weeks) or e-cigarette aerosol (1.8 mg/mL nicotine solution, 30 minutes/day for 30 days).* **Result:** *The results indicate that the BDNF levels in the conventional cigarette group were 1.27 higher than the control group, showing a relatively small difference. Meanwhile, the electronic cigarette group showed a significant increase in BDNF levels compared to the control group, 5.54 ($p = 0.01$), and the conventional cigarette group, 4.27 ($p = 0.009$). Histopathologically, the electronic cigarette group had a higher level of brain tissue damage (79 %) compared to the conventional cigarette group (75 %) and the control group (25 %).* **Conclusions:** *30 days of e-cigarette exposure significantly raised BDNF levels, with the control group showing the lowest. The e-cigarette group had the most severe brain damage, followed by the conventional cigarette group.*

Keywords: *Electronic cigarettes, conventional cigarettes, BDNF. histopathology; neurotoxicity.*

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ORCID: https://orcid.org/0009-0007-5827-4601[a]
ORCID: https://orcid.org/0000-0002-3492-0599[b]
ORCID: https://orcid.org/0000-0003-4125-005X[c]
ORCID: https://orcid.org/0000-0002-5240-4950[d]
ORCID: https://orcid.org/0000-0002-5160-8265[e]
ORCID: https://orcid.org/0000-0002-1385-9856[f]
ORCID: https://orcid.org/0009-0005-5649-0904[g]

[1]Magister Program in Biomedical Science, Postgraduate School of Hasanuddin University, Makassar 90245, Indonesia

[2]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar 90245, Indonesia

[3]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Hasanuddin University-Wahidin Sudirohusodo Hospital, Makassar 90245, Indonesia

[4]Department of Pathology Anatomy, Faculty of Medicine, Hasanuddin University, Makassar 90245, Indonesia

*Corresponding authors: Andhira Prabawati. E-mail: Prabawatiandhira@gmail.com

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RESUMEN

Objetivos: *Este estudio tiene como objetivo evaluar y comparar los efectos de la exposición al humo del cigarrillo electrónico y al humo del cigarrillo convencional sobre los niveles del Factor Neurotrófico Derivado del Cerebro (BDNF) y las características histopatológicas del cerebro en ratas.* **Métodos:** *24 ratas Wistar machos fueron divididas en tres grupos: un grupo de control (sin exposición al humo de cigarrillo) y dos grupos experimentales expuestos ya sea al humo de cigarrillo regular (1,8 mg de nicotina, 32 mg de alquitrán, 25 minutos/día durante 4 semanas) o al aerosol de cigarrillo electrónico (solución de nicotina 1,8 mg/mL, 30 minutos/día durante 30 días).* **Resultado:** *Los resultados indican que los niveles de BDNF en el grupo de cigarrillos convencionales fueron 1,27 más altos que en el grupo de control, mostrando una diferencia relativamente pequeña. Mientras tanto, el grupo de cigarrillos electrónicos mostró un aumento significativo en los niveles de BDNF en comparación con el grupo de control 5,54 (p = 0.01) y el grupo de cigarrillos convencionales 4,27 (p = 0,009). Histopatológicamente, el grupo de cigarrillos electrónicos tuvo un mayor nivel de daño en el tejido cerebral (79 %) en comparación con el grupo de cigarrillos convencionales (75 %) y el grupo de control (25 %).* **Conclusiones:** *30 días de exposición a cigarrillos electrónicos aumentaron significativamente los niveles de BDNF, siendo el grupo de control el que mostró los niveles más bajos. El grupo de los cigarrillos electrónicos tuvo el daño cerebral más severo, seguido por el grupo de los cigarrillos convencionales.*

Palabras clave: *Cigarrillos electrónicos; cigarrillos convencionales, BDNF, histopatología; neurotoxicidad.*

INTRODUCTION

The consumption of cigarettes continues to be a significant global health issue, impacting millions of people across diverse age demographics and geographical areas. Smoking, particularly via traditional cigarettes, entails inhaling tobacco smoke that comprises about 4 000 substances, including carbon monoxide, polycyclic aromatic hydrocarbons, and nicotine (1). Multiple studies have thoroughly recorded the detrimental health impacts of these drugs, including respiratory disorders, cardiovascular ailments, and numerous forms of cancer. Moreover, nicotine, being an addictive compound, poses significant risks to both active and passive smokers. Nicotine's addictive properties make a person physically dependent on it and damage the central nervous system (CNS), which could cause cognitive problems and changes in the brain (2).

The global prevalence of smoking is very concerning, with around 1.3 billion smokers worldwide, of which 942 million are men and 175 million are women. In Indonesia, which is the fifth-largest tobacco producer in the world, most adult smokers are men, with 65.9 % of men and 4.2 % of women aged 15 and above smoking (3,4). This widespread smoking habit demands efforts to address the associated health impacts, particularly those related to the brain.

The recent emergence of electronic cigarettes has introduced a new facet to the global smoking problem. E-cigarettes are battery-powered devices that vaporize a liquid containing nicotine, flavorings, and humectants such as propylene glycol or glycerol. E-cigarettes, promoted as a safer alternative to conventional cigarettes and a tool for smoking cessation, have gained significant appeal, especially among the youth. Although marketed as a safer option, evidence indicates that e-cigarettes still harbor detrimental components, including ultrafine particles and carcinogens, which can negatively impact health. The use of electronic cigarettes is often driven by trend attractiveness and the misconception that these devices present a lower danger compared to conventional smoking (5).

However, research on the potential neurotoxic effects of electronic cigarettes, particularly their impact on brain health, is still limited. Many people think that electronic cigarettes are safer than regular cigarettes, but there isn't much proof that they cause serious brain damage. This includes changes in brain-derived neurotrophic factor (BDNF) levels and brain histopathology. Given the increasing prevalence of e-cigarette use and its potential risks, it is crucial to investigate and compare the effects of exposure to e-cigarette and conventional cigarette smoke on brain health. This study aims to fill that gap by evaluating and comparing the effects of exposure to e-cigarette and conventional cigarette smoke on BDNF levels and brain histopathology in an animal experimental model such as rats. Understanding these effects will provide insights into the potential

neurotoxicity of electronic cigarettes, which can contribute to the debate over their safety.

MATERIALS AND METHODS

Study design and participants

This study employs a true experimental design, incorporating a pretest-post-test control group. A total of 24 male Wistar rats (150-200 g) were divided into three groups: the group exposed to conventional cigarettes, the group exposed to electronic cigarettes, and the control group. The rats were exposed to the smoke of conventional and electronic cigarettes for one month. Then, the Pharmacology and Toxicology Laboratory at Hasanuddin University, Indonesia, used the ELISA method to measure the levels of BDNF. Hasanuddin University's Educational Animal Hospital performed histopathological analysis to determine the extent of brain tissue damage.

Chemical and Smoke Preparation

Exposure to conventional cigarette smoke: this study used the brand Djarum Super Espresso 12. This cigarette contains 1.8 mg of nicotine and 32 mg of tar per stick. Nicotine and tar are the two main components in cigarette smoke that are known to have harmful effects on health, including negative impacts on the central nervous system and the potential to cause addiction. When it comes to exposure to the smoke from electronic cigarettes, the Joiway pod with Ice Berry variant liquid was used. The liquid contains 5 mL of nicotine in one pod container. This electronic cigarette's nicotine delivers effects akin to traditional cigarettes, albeit through the inhalation of vapor rather than smoke.

Animal Preparation

Male Wistar rats (150-200 g) were kept in the animal laboratory's Biofarmasi Laboratory, Hasanuddin University (Makassar, Indonesia). They were placed into plastic cages with adequate ventilation, with a maximum of 4 rats per cage, at a controlled room temperature, a 12-hour light-dark cycle, and free access to water and food for all animals. The rats underwent an acclimatization period of at least 7 days before participating in the experiment.

Experimental Protocol

Rats underwent exposure to conventional cigarettes during the experimental stage. The rats were exposed to one cigarette smoke daily for less than 30 minutes. Meanwhile, the rats exposed to electronic cigarettes received 1.8 mL of electronic cigarette liquid each day for the same duration. The exposure was conducted continuously for 30 consecutive days. Rats were killed by decapitation, and on the 31st day, the brain was dissected to obtain samples of the right brain tissue, which was preserved with liquid nitrogen. At the HUMRC RS Hasanuddin University Laboratory, the ELISA method measured the BDNF levels in the right brain tissue samples. Meanwhile, the Faculty of Veterinary Medicine at Hasanuddin University, Makassar, Indonesia, analyzed the histological preparations of the left-brain tissue.

Biomarker Analysis

The protocol for quantification of BDNF levels in tissue using the BT LAB brand ELISA kit was initiated with tissue preparation. The tissue was washed with phosphate-buffered saline (PBS) (pH 7.4) to remove any remaining blood. It was then weighed and mixed with PBS in a glass homogenizer on ice to keep the proteins stable. Cells in suspension were lysed through repeated freeze-thaw cycles or by sonication. The obtained homogenate was centrifuged at 12 000 rpm for 15 minutes at 4°C to separate the supernatant, which was used as the test sample. The supernatant was used directly or stored at -80°C to maintain protein integrity before analysis. The ELISA test was conducted by adding the tissue supernatant to the BT LAB ELISA plate coated with BDNF-specific antibodies. The process continued by adding biotinylated antibodies and Streptavidin-HRP to form the antigen-antibody complex, followed by incubation for 60 minutes at 37°C. After incubation, the plate was washed five times to remove unbound reagents. Substrate solutions A and B were added, resulting in a color change due to the enzymatic reaction, and

the plate was re-incubated for 10 minutes in the dark. The reaction was stopped with a stop solution, causing the color to change from blue to yellow. The absorbance value was measured using a microplate reader at a wavelength of 450 nm. The concentration of BDNF in the tissue was calculated based on the standard curve created using the standard solution from the BT LAB kit.

Histological Assessment

The results of the brain injury scoring calculations are illustrated in Figure 1. The brain was extracted from the prefrontal cortex, subsequently removed and rinsed in cold phosphate-buffered saline (PBS) and then fixed in 10 % formaldehyde for 48 hours. The samples were then placed through a tissue processor, covered in paraffin wax, and cut into five µm thick slices with a microtome. Hematoxylin and eosin (H&E) stain the tissue sections. Professionals and veterinarians conduct this procedure at the Educational Animal Hospital of the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

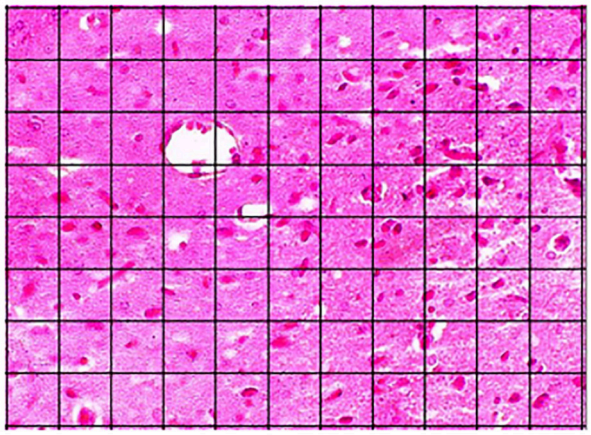

Figure 1. Histopathological damage score analysis using ImageJ software at 40x magnification. This analysis entailed dividing each histology image into many tiny squares, arranged in 11 vertical rows and eight horizontal columns, yielding a total of 88 squares. We assign one rating to each box displaying signs of tissue damage. Using the appropriate calculation, we calculate the percentage of network damage by comparing the number of damaged boxes to the total number of boxes. Next, we calculated the percentage of damage using the following formula: Percentage of Damage = (amount of damage observed / total possible damage) × 100 %

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 25.0. Normality was assessed using the Shapiro-Wilk test. Statistical comparisons were performed using the Student's t-test and one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. The data were presented as mean ± standard deviation. A difference was considered statistically significant when $p<0.05$.

RESULTS

Table 1. Comparison of Weight Gain between Groups

		Mean±SD	Difference±SD	IC95 %	p-value
Control (n=5)					
	Baseline	107.8 ± 17.02	101.4 ± 34.5	58.5 – 144.2	0.003*
	Week-4	209.2 ± 34.39			
CS (n=5)					
	Baseline	137.4 ± 5.77	94.8 ± 13.5	77.9 – 111.6	0.001*
	Week-4	232.2 ± 15.49			
ES (n=5)					
	Baseline	122.8 ± 5.45	98.2 ± 24.08	68.3 – 128.1	0.001*
	Week-4	221.0 ± 24.8			

CS, conventional cigarette smoke-exposed group; ES, e-cigarette smoke-exposed group.
*Statistically difference ($p<0.05$).

Body Weight

Table 1 shows a notable rise in average body weight among the rats across all groups during a 30-day treatment period. The control group showed a significant increase in body weight, from 107 ± 17.02 grams to 209.2 ± 34.3 grams, with a p-value of 0.003 ($p < 0.05$) and a difference of 101.4 (95 % CI: -144.2 to -58.8). The weight of the animals who received electronic cigarettes exposure increased from 122.8 ± 5.45 grams to 221.8 ± 24.8 grams, with a p-value of 0.003 ($p<0.05$) and a difference of 98.2 (95 % CI: -128.1 to -68.3). The conventional cigarette group had the most significant increase, raising the body weight from 137.6 ± 5.7 grams to 232 ± 15.4 grams, with a p-value < 0.001 ($p < 0.05$) and a difference of 94.8 (95 % CI: -111.6 to -77.9). Body length was also augmented in all groups. Regarding brain weight, the group that smoked regular cigarettes had the highest average brain weight (1.4 ± 0.35 grams), followed by the group that smoked electronic cigarettes (1.3 ± 0.29 grams) and finally, the control group (1.2 ± 1.5 grams). Thus, there were no significant differences between the groups ($p = 0.519$).

Brain Tissue Level of Brain-Derived Neurotrophic Factor (BDNF)

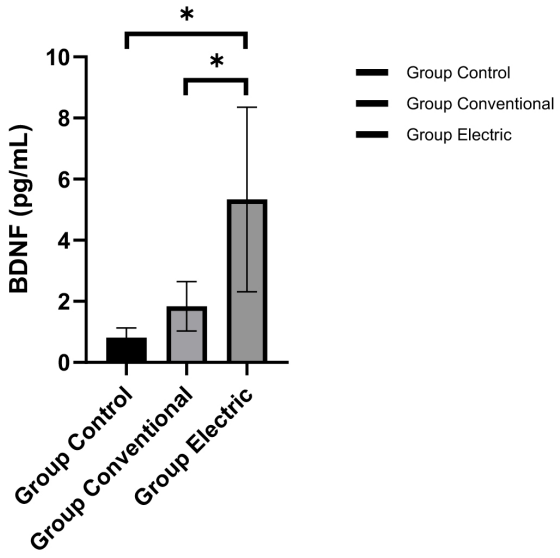

Figure 2. The brain-derived neurotrophic factor (BDNF) levels in the control group, conventional cigarettes, and electronic cigarettes.

Figure 2 shows that the control group exhibited the lowest levels, averaging 1.93 ± 0.93 pg/mL, whereas the electronic cigarette group demonstrated the highest levels, averaging 8.00 ± 2.80 pg/mL. The traditional cigarette cohort exhibited an average concentration of 3.20 ± 1.67 pg/mL. This data indicates that BDNF levels in the e-cigarette group are significantly higher than those in the control group (mean difference = 5.54; $p = 0.01$) and the traditional cigarette group (mean difference = 4.27; $p = 0.009$). In contrast, the BDNF levels between the conventional cigarette and control groups do not exhibit a significant difference (mean difference = 1.27; $p = 0.546$).

This data indicates that exposure to electronic cigarettes markedly elevates BDNF levels in comparison to both the control group and the conventional cigarette group. This suggests that electronic cigarettes had a more pronounced effect on elevating BDNF levels than conventional cigarettes or no exposure, with a significant threshold of $p < 0.05$.

Histopathological examination

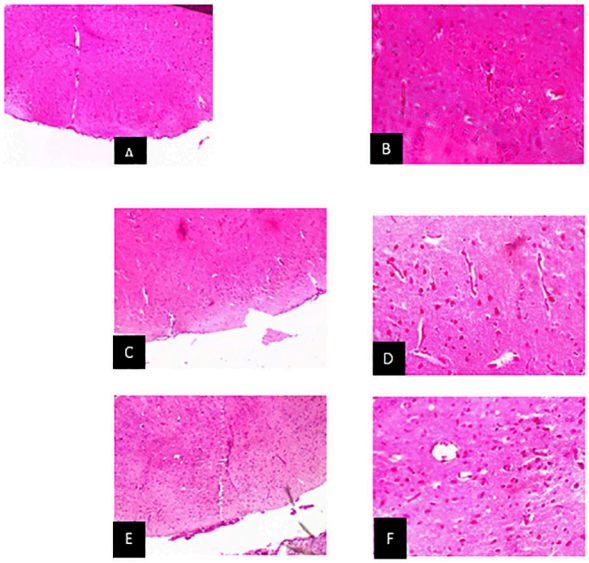

Figure 3. The results of histological analyses of the prefrontal cortex at magnifications of 10x and 40x across three groups: The control group (A and B) displayed normal brain tissue architecture without intervention, with 25 % damage noted. In the typical conventional cigarette group (C and D), tissue damage increased by nearly 75 %, along with significant histological changes. The electronic cigarette group (E and F) had the most pronounced cerebral tissue damage, with impairment above 79 % and more evident structural changes. The specified areas exhibit necrotic damage.

The histopathological scoring of the images is divided into 88 small boxes, each of which indicates tissue damage and receives a single score. The percentage of damage is calculated using the formula: (number of damaged boxes / 88) × 100 %. Figure 3 shows the brain histopathology scores from three treatment groups: control, conventional cigarette, and electronic cigarette. In the control group, the histopathology score was 22, with a damage percentage of 25 %. In the conventional cigarette treatment group, the histopathology score increased to 66, with a damage percentage of 75 %. Meanwhile, in the electronic cigarette treatment group, the histopathology score was the highest, at 70, with a damage percentage of 79 %. This data indicates that the groups exposed to cigarettes, both conventional and electronic, had higher histopathology scores and brain damage percentages compared to the control group.

DISCUSSION

Nicotine exposure from cigarette smoke inhibits appetite via cerebral processes, resulting in an energy deficit characterized by reduced intake and heightened energy expenditure. After seven days, this induces weight loss, especially in abdominal fat mass, which is linked to the risk of glucose intolerance and insulin resistance (6,7).

The research indicates variations in average weight change between the baseline assessment and the fourth week across each group. In the control group, body weight increased from 107 ± 17.02 grams to 209.2 ± 34.3 grams, reflecting a weight gain of 102 grams. The electronic cigarette group increased from 122.8 ± 5.45 grams to 221.8 ± 24.8 grams, resulting in a gain of 99 grams. The conventional cigarette group demonstrated the most significant increase, from 137.6 ± 5.7 grams to 232 ± 15.4 grams, corresponding to a gain of 95 grams. The findings show that the groups exposed to regular and electronic cigarettes gained weight less quickly than the control group. This suggests that cigarette smoke exposure affects metabolism function.

The brain reacts to fluctuations in energy balance by modifying food consumption levels. Neuropeptides in the hypothalamus are essential for regulating food intake, modulating their activity by circulating hormones like leptin (8). The way nicotine interacts with NPY shows how it affects hypothalamic appetite control. Indeed, NPY, a 36-amino acid neuropeptide, is abundant in the brain of rats and is highly concentrated in the hypothalamus. NPY administration is potently orexigenic, and expression of NPY mRNA in the arcuate nucleus is increased in response to fasting or chronic but moderate food restriction. A simple prediction is that if NPY signaling is a target for nicotine's anorectic action, then nicotine treatment might suppress the expression of NPY or NPY receptors. In the short term, this appears to be true. It was found that acute (24-h) nicotine administration reduced food intake by 30 % and lowered NPY

and NPY mRNA levels in the arcuatus nucleus by 35 %. This suggests that nicotine centrally helps to reduce appetite and weight (9). Smoking has a significant effect on the concentrations of neurotransmitters in the brain. Nicotine affects the release of neurotransmitters such as dopamine, norepinephrine, and acetylcholine. Previous studies demonstrated that the elevation of extracellular neurotransmitters, including dopamine and glutamate, was linked to neurobehavioral changes in animals exposed to substances of abuse, including nicotine. Dopamine, in particular, is strongly linked to the rewarding and reinforcing effects of smoking, and nicotine increases dopamine release in the synaptic cleft. This leads to increased well-being feelings, reward, and reinforcement, which contribute to the development of nicotine dependence (10). Short-term exposure to cigarette smoke results in weight loss, diminished food intake, lower fat mass, and a decline in plasma leptin levels (11) carbon dioxide, and nitric oxide - the three-gas respiratory cycle - that insures adequate oxygen and nutrient delivery to meet local metabolic demand. In this context, it is blood flow and not blood oxygen content that is the main driver of tissue oxygenation by red blood cells (RBCs). Herein, we review the lines of experimentation that led to this understanding of RBC function; from the foundational understanding of allosteric regulation of oxygen binding in Hb in the stereochemical model of Perutz, to blood flow autoregulation (hypoxic vasodilation governing oxygen delivery). Smoking activities not only impact physical health but also significantly affect brain function and health. One of the main components in cigarettes, nicotine, is known to have neurotoxic effects that can disrupt cognitive function (12).

Biologically active BDNF is a dimer consisting of two identical peptide chains held together by noncovalent interactions; of all neurotrophins in mature CNS, BDNF is the most abundantly expressed, directly supporting the survival and maintenance of function of many types of neurons and hippocampal aging and differentiation. It is widely accepted that BDNF stimulates neurogenesis, which is associated with the relationship between adult hippocampal neurogenesis and BDNF. Enhanced hippocampal neurogenic capacity has been related to increased BDNF levels, resulting in improvements in hippocampus-dependent memory. Cigarettes can influence brain-derived neurotrophic factor (BDNF) concentrations in the brain. It is known that dopamine activates pathways that help neural connections, which elevate BDNF levels, which are crucial for the well-being of neuronal cells, especially in the hippocampus (13). The elevation of BDNF facilitates the formation and reinforcement of neuronal connections; hence, it enhances cognitive function (14).

Upon inhalation of cigarette smoke, nicotine is rapidly absorbed through the alveolar walls of the lungs into the bloodstream, subsequently traversing the blood-brain barrier to access brain tissue (15). Nicotine binds to nicotinic acetylcholine receptors (nAChRs) in the brain, mainly in the hippocampus, prefrontal cortex, and ventral tegmental area (VTA). This induces the release of neurotransmitters like serotonin, dopamine, and glutamate (16). Dopamine secretion in the mesolimbic pathway induces bliss, whereas glutamate, an excitatory neurotransmitter, enhances synaptic connections (17). Li et al. (2023) state that this pathway elevates the concentration of brain-derived neurotrophic factors (BDNF). BDNF facilitates neuronal adaptation and enhances synaptic efficacy (18).

Cigarette smoke induces an oxidative stress response in the brain. Cigarette smoke comprises harmful substances that produce reactive oxygen species (ROS), potentially damaging neurons. The brain elevates BDNF expression as a protective mechanism to safeguard nerve cells from injury. The BDNF helps neurons stay alive and heals damaged tissue (17,19). The increase in BDNF levels in the brains may protect against the adverse effects of being exposed to dangerous substances (20).

The findings indicated a considerable change in BDNF levels among the groups. The mean BDNF level in the control group was 0.93 ± 0.30; in the conventional cigarette smoke exposure group, it was 2.20 ± 0.80; and in the electronic cigarette smoke exposure group, it was 2.59 ± 3.1. Findings show that groups exposed to both regular and electronic cigarette smoke had higher levels of BDNF compared to the control group. The average value for the electronic cigarette group was the highest ($p < 0.05$).

The increase in BDNF levels, although initially advantageous, may ultimately strengthen circuits that perpetuate smoking behavior over time. The neuroadaptation process alters the brain's structure, enhancing its receptivity to nicotine's effects and reinforcing the memories and pleasurable emotions associated with smoking. Consequently, the brain's modifications that encourage addictive behavior hinder the quitting of smoking (21).

Cigarettes, both conventional and electronic, may negatively impact on the histopathological state of the brain. Smoking cigarettes exposes individuals to numerous detrimental substances that might induce oxidative stress, a condition characterized by the excessive production of free radicals and insufficient neutralization of these radicals. Oxidative stress can activate signaling pathways, such as NADPH oxidase, which generates increased levels of superoxide (O^{2-}), a detrimental compound that damages cell membranes, proteins, and neuronal DNA. The nicotine in cigarettes can alter neurotransmitters, impairing the functionality of synapses. This may result in the death of neuronal cells, particularly in critical regions such as the prefrontal cortex, associated with cognition and behavior. There is an increase in the mortality of pyramidal cells and alterations in their morphology, indicating structural and functional damage to brain tissue (22-25).

The histopathology results reveal a greater impact from both electronic and regular cigarette smoke compared to the non-smoking control group. The scoring data from ImageJ software demonstrates this. The control group exhibited a histopathological score of 22 and a damage proportion of 25 %, signifying a largely normal tissue state. The traditional cigarette group exhibited a histopathological score of 66, with a damaged percentage of 75 %, indicating considerable tissue injury. At the same time, the group that used electronic cigarettes had the highest histopathology score of 70, which means that 79 % of the tissues were damaged, which is a more severe level of injury. The study shows that cigarette smoke, especially from electronic cigarettes, damages brain tissue more than smoking regular cigarettes or being in a control group. The study demonstrates histological scoring of the brain region, which aligns with the BDNF value findings.

This study shows that breathing in the smoke from electronic cigarettes is much worse for the brain than smoking regular cigarettes. The damage is worse than in the control group, where brain tissue conditions were mostly normal.

CONCLUSION

This study demonstrates that exposure to electronic cigarette smoke for 30 days markedly elevates Brain-Derived Neurotrophic Factor (BDNF) levels relative to the control group and conventional cigarettes yet is associated with more pronounced histopathological damage to brain tissue (79 %) compared to the conventional cigarette group (75 %) and the control group (25 %). The elevation in BDNF levels serves as a neuroprotective compensatory response to damage caused by exposure to hazardous agents in electronic cigarette smoke. These data suggest that, although being perceived as safer, electronic cigarettes may exert a greater neurotoxic effect than traditional cigarettes.

Conflict of interest

The authors declare no conflict of interest

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