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Original Article

Development of Rapid Electrical Kindling by Copper and Stainless Steel Electrodes: A Comparative Evaluation

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Abstract
Electrical kindling is a popular model for studying epilepsy, which is similar to complex focal seizures in humans. In this method, by implanting metal electrodes in the brain and subthreshold stimulation, the animal acquires chronic convulsions. This study aimed to compare the development of rapid electrical kindling using steel and copper electrodes in adult male Wistar rats. Tri-polar steel or copper electrodes and two unipolar electrodes were stereotaxically embedded in the basolateral nucleus of the amygdala or the skull surface, respectively. One week later, the threshold current intensity was determined. Twenty-four hours afterward, animals received six stimulations per day with the threshold intensity until they showed three consecutive stage five seizures. The animals were then perfused, and their brains were fixed, stained, and examined histologically. The results showed that animals with the steel electrode had a significantly lower threshold than those with a copper electrode. In addition, the number of stimulations for seizure generalization was significantly lower in the steel group. The amount of tissue damage in the experimental groups was not significantly different; however, the number of dead cells in the steel groups was significantly lower than that in the copper groups. In conclusion, although animals were kindled with copper electrodes, they may not be suitable for use in laboratory evaluations due to the neurotoxic effects of copper, which lead to tissue damage and delays in seizure parameters. Therefore, the results of such studies can be misleading.

Keywords: Electrode, Epilepsy, Rapid electrical kindling, Seizure

Background

Epilepsy is a brain syndrome with a high rate of occurrence. Unfortunately, about 30% of epileptic patients are refractory to antiepileptic drugs [1]. Therefore, various experimental models of epilepsy have been established in an attempt to discover new effective antiepileptic drugs. Electrical kindling is a putative experimental model of epilepsy which was initially introduced by Goddard [2] and has been widely used for this purpose. This model of epilepsy is equivalent to human complex focal seizures. To establish kindled animals, usually stainless steel electrodes are implanted in some brain areas of experimental rodents. After determination of the threshold intensity, the animals receive either a single electric current each day [3] or various currents each day [4] to reach stage five seizures in Racine classification [5]. The later-named rapid kindling has the advantage of fast development of the kindling process, usually within three to five days. The problem is that the stainless steel wires used to make the electrodes are rather expensive. Copper, on the other hand, is a relatively low-cost and readily available metal that is used to make electric wires. Accordingly, it may be used as an alternative to steel electrodes in the development of the rapid electrical kindling model of epilepsy. In animal cells, copper is a crucial element and functions as a cofactor for vital enzymes. Both copper insufficiency and surplus have detrimental impacts on cells and organisms [6]. As a case in point, cellular copper excess was shown to have exceedingly damaged the mitochondria [7]. Accordingly, cells use mechanisms to keep copper concentrations in an appropriate range. The brain contains the highest content of copper after the liver [8]. Meanwhile, it was reported that the brain mitochondria are especially vulnerable to copper [9]. Interestingly, patients with mesial temporal lobe

epilepsy showed a considerably lower copper level in their hippocampus [10]. On the other hand, in the electrical kindling model, just the tip of the tri-polar electrodes is in direct contact with the neurons, and the effect of such contact on neurons and the induction of subsequent seizures has not been well studied, specifically in the rapid kindling model. Therefore, this study aims to compare the development of rapid electrical kindling in rats, using stainless steel and copper electrodes.

Objectives

This study aimed to compare the development of rapid electrical kindling using steel and copper electrodes in adult male Wistar rats.

Materials and Methods

Animals

Twenty-four adult male Wistar rats (300±20 g) were used in this study. They were four months old and were provided by the animal breeding center of the Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran. The animals were kept under standard protocol conditions. The study received an ethics code from the Ethics Committee of University of Isfahan, Isfahan, Iran (Code No. IR.UI.REC.1401.058). Water and food were freely available for the animals. They were kept in standard cages (42cm×26.5cm×15cm). The animal room had a persistent temperature (21±1°C) and a 12/12 light/dark period (light on at 7 a.m.).

Establishment of the Electrical Kindling

Rats were divided into four groups (n=6) arbitrarily. The electrical kindling method was performed as defined previously [11]. Animals were anesthetized with ketamine (100 mg/kg; i.p) and xylazine (10 mg/kg; i.p) and put in the stereotaxic apparatus to implant a tri-polar electrode in the right basolateral amygdala nucleus (AP: -2.5 mm from the bregma; ML: -4.8 mm from the bregma; DV: -7.5 mm from the dura) [12]. Two unipolar electrodes were fixed on the right and left parietal bones. After one week of recovery, the electrical current was delivered to the amygdala using a stimulator device (e-Pulse, Science Beam, Tehran, Iran). An amplifier (e-Wave, Science Beam, Tehran, Iran) was used to record and determine the after-discharge (AD) threshold. After 24 h, animals got six stimulations each day with 20-min intervals until they showed three successive stage five seizures along with the Racine classification [5].

Histological Preparations

The histological preparations were performed as described earlier [13]. In brief, the perfusion was conducted with phosphate-buffered saline, followed by 4% paraformaldehyde, in three rats from each group. Next, the brains were removed, held in 4% paraformaldehyde, and fixed in paraffin. Suitable coronal sections were then prepared from the amygdala. The Nissl method was used to stain brain sections and quantify dead neurons in the basolateral amygdala. The 0.1% Cresyl Fast Violet was used to stain cellular nuclei (Merck, Germany). Three visual microscopic fields were chosen to provide digital images from the amygdala. The amygdala dead neurons were measured by Image J software.

Statistical Analysis

The Shapiro-Wilk and Kolmogorov-Smirnov tests were utilized to examine the distribution of the data. Unpaired t-test or one-way analysis of variance (ANOVA) was used to analyze the data. The Data were analyzed using GraphPad Prism (version 9.0.1). The results were shown as mean±SEM. A P-value of <0.05 was considered statistically significant.

Results

Effect of Stainless Steel and Copper Electrodes on Threshold Intensities

The unpaired t-test results showed that the threshold intensities were significantly lower in animals implanted with stainless steel electrodes compared to the group implanted with copper electrodes (P=0.02). However, after-discharge duration (ADD) in the threshold did not vary between the experimental groups (P=0.28) (Figure 1).

Effect of Stainless Steel and Copper Electrodes on Generalization of the Seizures

The unpaired t-test results indicated that the number of stimulations required to reach stages two (P=0.08), four (P=0.05), and five (P=0.07) did not differ significantly in the stainless steel or copper electrode implanted groups. However, the number of stimulations to reach stage three (the first generalized stage) was significantly lower in the stainless steel group than in the copper group (P=0.01) (Table 1).

Effect of Stainless Steel and Copper Electrodes on Seizure Parameters in Fully-Kindled Rats

The unpaired t-test indicated that seizure parameters, including ADD (P=0.14), stage four latency ([S4L], P=0.46), and stage five duration ([S5D], P=0.45) did not vary significantly in fully kindled rats between the stainless steel group and the copper electrode group (Figure 2).

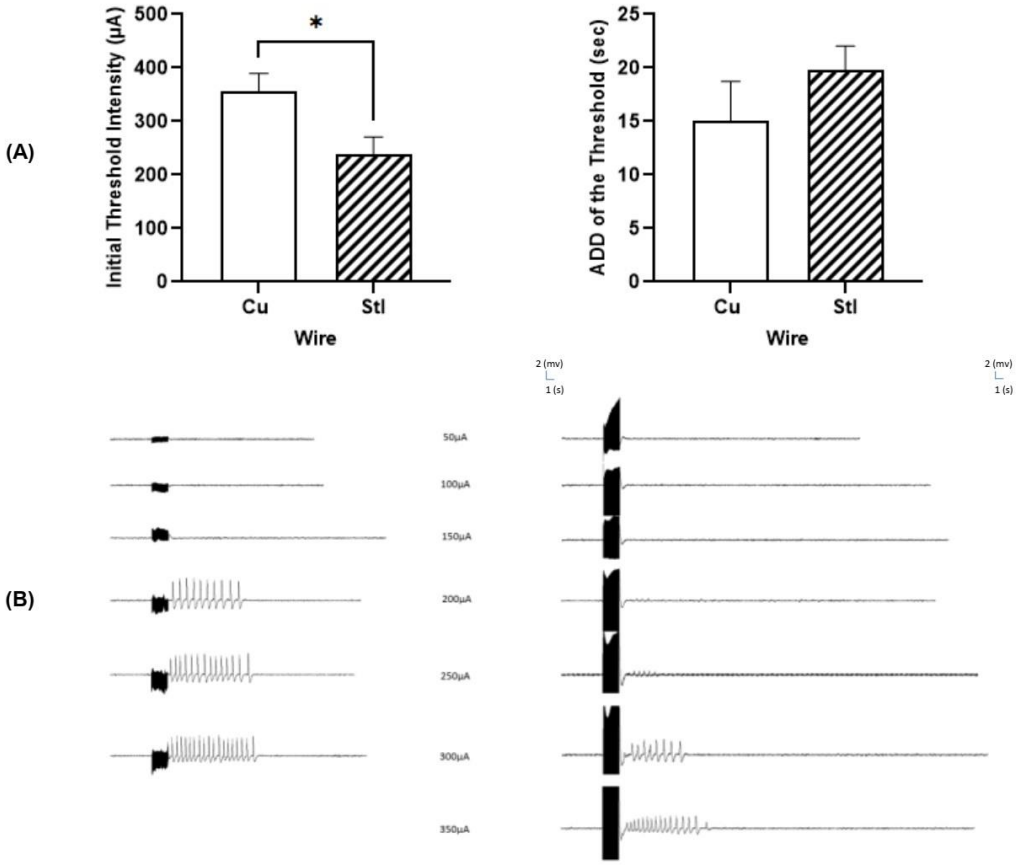

Figure 1. Determination of the threshold intensity. (A) The unpaired t-test results showed that the threshold intensity was significantly lower in the stainless steel group compared to the copper group. However, the ADD of the threshold did not differ between the experimental groups. (B) Representative ADs were recorded from the basolateral amygdala to determine the threshold intensity. The initial stimulation intensity was 50 µA, which was augmented in steps of 50 µA every five minutes in anticipation of recording a 20-sec AD. Data are expressed as mean±SEM.
*P<0.05
ADD: After-discharge duration
AD: After-discharge
SEM: Standard error of the mean

Table 1. Effect of stainless steel and copper electrodes on generalization of the seizures

Variables	Groups	Mean	SEM	P-Value
NS to stage 2	Cu	9.37	2.82	0.08
	Stl	4.00	0.59	
NS to stage 3	Cu	21.13*	4.24	0.01
	Stl	8.25	0.99	
NS to stage 4	Cu	22.86	2.98	0.05
	Stl	14.00	2.99	
NS to stage 5	Cu	34.29	4.18	0.07
	Stl	22.75	4.33	

The unpaired t-test results showed that the number of stimulations required to reach stage three was significantly lower in the stainless steel group compared to the copper group.
*P<0.05
SEM: Standard error of the mean
Cu: Copper
Stl: Steel
NS: Number of stimulations

Effect of Stainless Steel and Copper Electrodes on the Extent of Injury in the Basolateral Amygdala

One-way ANOVA results revealed that there was no significant difference in the extent of injury in the amygdala between experimental groups (P=0.08) (Figure 3).

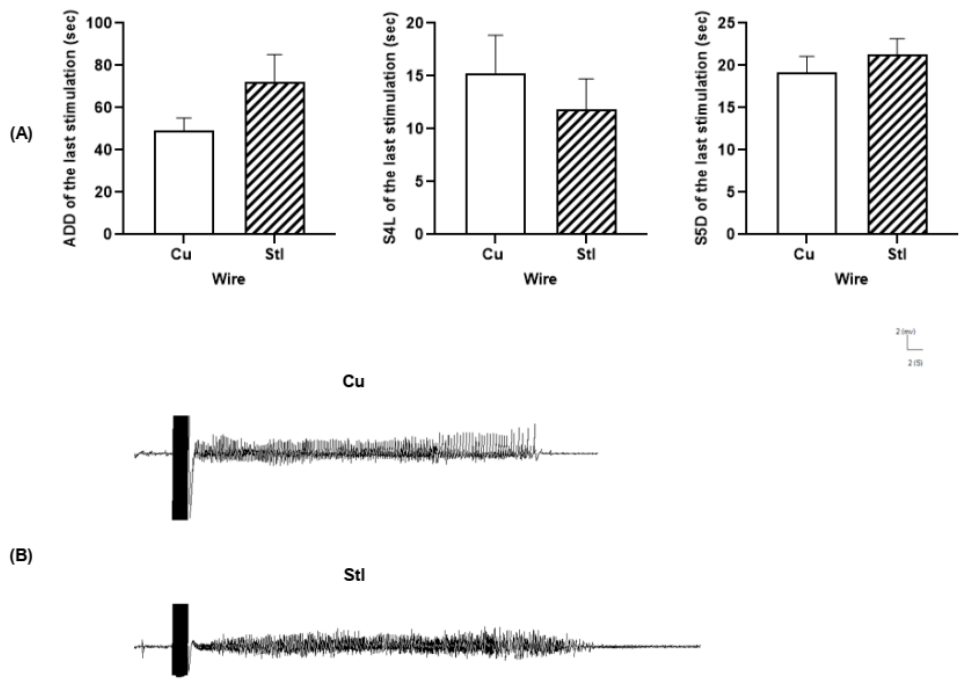

Figure 2. Seizure parameters in fully-kindled rats. (A) After the establishment of the kindling, seizure parameters, including ADD, S4L, and S5D, did not differ significantly in rats implanted with stainless steel electrodes compared to those implanted with copper electrodes. (B) Represented ADs in the fully kindled rats in either of the stainless steel or copper electrode groups. Data are expressed as mean±SEM.
ADD: After-discharge duration
S4L: Stage four latency
S5D: Stage five duration
AD: After-discharge
SEM: Standard error of the mean

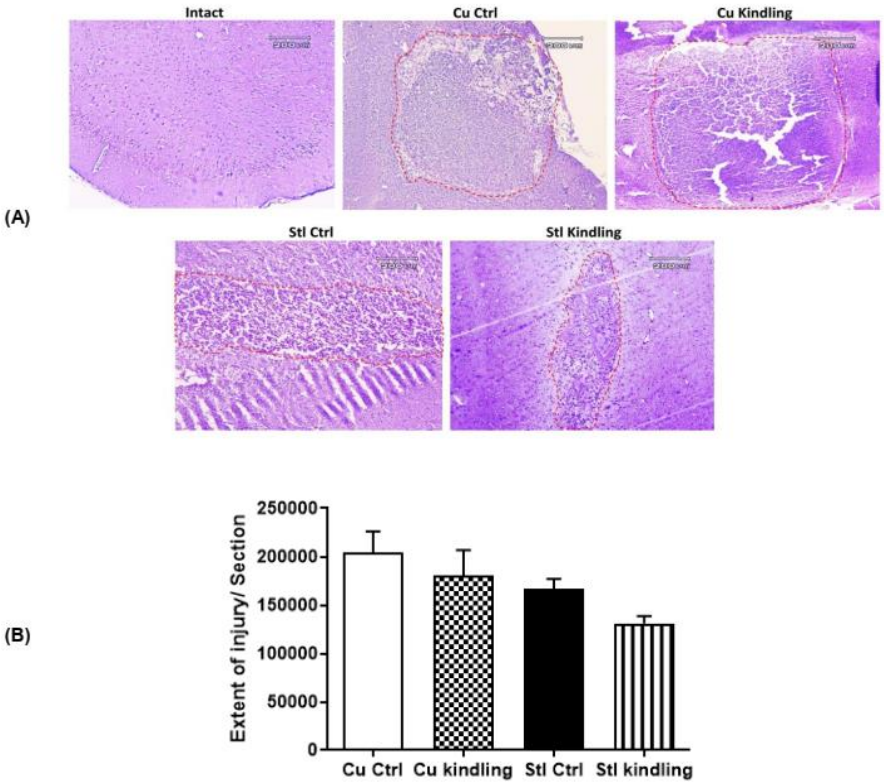

Figure 3. (A) Qualitative and (B) quantitative analysis showing the extent of injury in the basolateral amygdala. Three rats from each group were used for histological evaluations. One-way ANOVA results showed that there was no significant difference in the extent of injury between the experimental groups. Data are expressed as means±SEM.
ANOVA: Analysis of variance
SEM: Standard error of the mean

Effect of Stainless Steel and Copper Electrodes on the Number of Dead Cells in the Basolateral Amygdala

One-way ANOVA results revealed that the number of dead cells in the amygdala altered significantly in the experimental groups. The Tukey-Kramer post hoc test displayed that the number of dead cells was significantly lower in the steel control group than in the copper control group (P<0.01) and in the steel kindled group than in the copper kindled group (P<0.05). In addition, the number of dead cells was lower in the steel control and steel kindled groups than in the copper control group (P<0.001) (Figure 4).

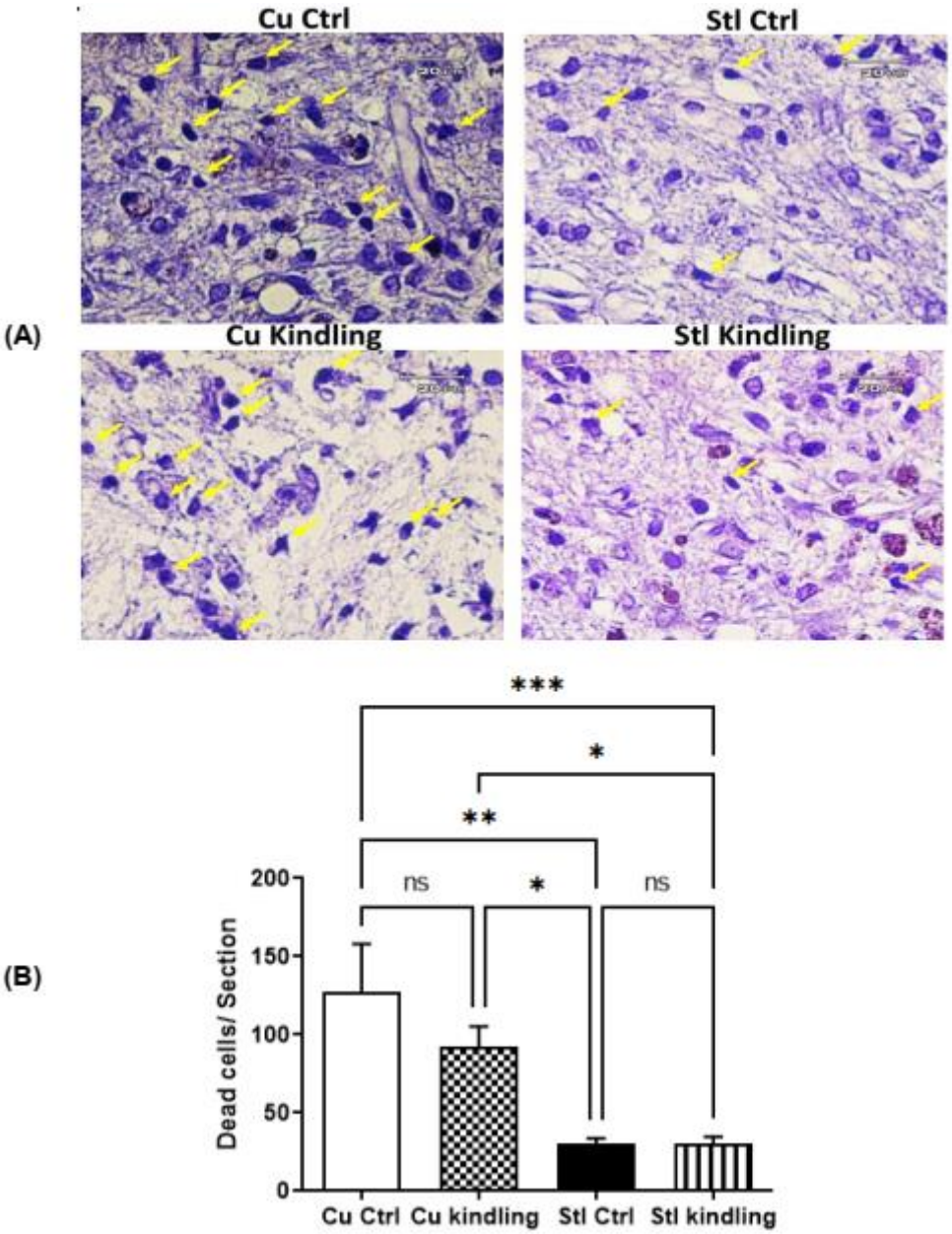

Figure 4. The number of dead cells in the basolateral amygdala of the experimental groups. Three rats from each group were used for histological evaluations. One-way ANOVA results showed that there was a significant difference in the number of dead cells in the amygdala in the experimental groups. The Tukey-Kramer post hoc test showed that the number of dead cells was significantly lower in the steel control group compared to the copper control group (P<0.01) and in the steel kindled group compared to the copper kindled group (P<0.05). Data are expressed as means±SEM. Arrows indicate dead cells. Scale bar: 20 µm.
*P<0.05, **P<0.01, ***P<0.001
ANOVA: Analysis of variance
SEM: Standard error of the mean

Discussion

The results of this study revealed that animals with a steel tri-polar electrode in their amygdala had a significantly lower threshold than those with a copper electrode. However, the ADD of the threshold did not vary between the experimental groups. The lack of a significant difference in the ADD of the threshold was because the criterion for threshold determination was the occurrence of at least 20 min of AD for all the experimental groups.

Therefore, the animals in all groups were stimulated with different intensities until they showed at least 20 min of AD, and the group with copper electrodes reached this criterion at the expense of a higher threshold.

The intracranial electrodes are commonly used to record electrical potentials elicited by neurons. An investigation of the electrical characteristics of different metals showed that silver chloride and copper were reasonable for this purpose. However, silver, gold, platinum, and stainless steel reduced very low frequencies, which made the recordings problematic. Therefore, from this perspective, silver chloride and copper were shown to be desirable [14]. Later, it was shown that rats implanted with nichrome wire to induce electrical kindling had significantly lower AD thresholds and required fewer stimulations to produce stage five convulsions compared to the group implanted with copper electrodes. The authors concluded that this might have occurred due to neural damage by copper electrodes that retarded the kindling process. However, they did not find any obvious histological injuries [15]. Our findings are consistent with the findings of that study, as rats with steel electrodes had lower thresholds than the copper electrode group, while there was no significant difference in the extent of injury in the amygdala of the experimental groups. However, they used the traditional kindling protocol, which uses a single electrical stimulation/day and needs much longer (up to 30 days) to develop kindling epileptogenesis. Given that in the rapid kindling protocols, the animals are fully kindled in short periods of three to five days, we thought that copper electrodes might be suitable to be used as an alternative to high-cost stainless steel electrodes for the establishment of rapid electrical kindling. It was reported that prolonged stainless steel electrode implantation into the rat amygdala decreased threshold intensity and increased the rate of kindling, which was attributed to the iron deposition and long-lasting biochemical alterations in neuronal cells adjacent to the tip of the electrodes [16, 17]. By contrast, the long-period implantation (up to 37 days) of copper electrodes in the rat brain caused necrosis and phagocytosis [18]. Meanwhile, some studies have proposed that kindling is the consequence of tissue injury triggered by the kindling process [19]. Wolske et al. suggested that this injury could not be due to the necrotic and phagocytic injuries caused by copper electrodes [15]. Our histological evaluations indicated that the number of dead cells was significantly different in the control groups implanted with steel or copper electrodes not receiving stimulation. In addition, the number of dead cells in the steel control and steel kindled groups was almost the same. This may reflect the fact that kindling by itself did not induce neuronal death, and the copper electrode was responsible for killing the neurons.

In our study, generalization of the kindled seizures was delayed in rats with the copper electrodes, as shown by the augmented number of stimulations to show stage three. This may reflect the reduced number of neurons in the seizure focus (basolateral amygdala). However, after the establishment of the kindling epileptogenesis, seizure parameters, including ADD, S4L, and S5D, did not vary in either of the experimental groups. This may be because the tip of the copper electrode affected only neurons in the seizure focus (basolateral amygdala) and left those outside the seizure focus intact.

Recent studies have proposed a role for copper in neuronal excitability, showing that copper affects neurotransmission in the rat brain [20]. Copper ions release at synapses and modulate synaptic activity and excitotoxic cell death. Despite the neurotoxic activities of copper, the release of endogenous copper in the synapse and the administration of exogenous copper were shown to defend primary neurons of the hippocampus from N-methyl D-aspartate (NMDA)-induced cell death [21], which might relate to the action of copper as an NMDA receptor non-competitive antagonist [22].

Meanwhile, neurotransmitter receptors are potential targets for copper. Copper has been shown to inhibit $GABA_A$ ionotropic receptors in neurons of the cerebellum [23]. Studies showed that copper antagonized P2X4, the most widely distributed purinergic receptor in the rat brain, which increased brain excitability. It had a biphasic effect on glutamate NMDA, and AMPA receptors. Acute treatment of the hippocampal neurons with copper inhibited AMPA receptor-mediated neuro-transmission, while the chronic application of copper increased functional AMPA receptors [24]. The same biphasic effect was reported for NMDA receptors in the neonatal rat cerebellum [25]. In addition, high levels of copper suppressed the NMDA receptor subunit GluN2B level in the hippocampus, impaired synaptic function, and triggered memory dysfunction in stressed mice [26]. Whether the tip of the copper electrodes had the same effect on neurotransmitter receptors in the amygdala needs to be clarified in future studies. However, it is probable that the lack of neurons and the delay in the development of the kindling epileptogenesis might have occurred somehow due to the effect of the copper electrode on increased excitability induced by the inhibition of $GABA_A$ or P2X4 receptors or glutamate receptor-induced

excitotoxicity.

Electrical kindling is a model of synaptic plasticity and resembles long-term potentiation (LTP). Kindling is accompanied by a rise in excitatory mechanisms, specifically a rise in the quantity of glutamate binding sites that are assumed to be a category of glutamate receptors. Likewise, LTP is provoked by transitory bursts of electrical stimulation in excitatory pathways and is accompanied by a rise in the quantity of the identical type of glutamate binding sites [27]. Interestingly, the former induction of LTP in the perforant path was shown to facilitate the establishment of electrical kindling [28], while electrical kindling impaired synaptic plasticity [29]. LTP was revealed to be inhibited in hippocampal slices exposed to exogenous copper [30, 31] and in rat hippocampal slices that received a high-copper diet [32]. However, copper was required for amygdala LTP [33]. These discrepancies in different studies highlight the need to assess the effect of copper electrodes in different neuroscience methods. However, based on the resemblance of kindling with LTP, it is likely that copper electrodes retarded the kindling parameters by impairing LTP in the brain circuitry involved in amygdala rapid kindling.

It is worth noting that in the electrical kindling model of epilepsy, each animal serves as its own control. From this point of view, one might think that it is likely to establish full-kindled animals with copper electrodes and use kindled animals for experimental purposes. Although the tip of the electrodes is only in contact with the adjacent neurons, and in fully-kindled rats, seizure parameters were not significantly different compared to rats kindled with steel electrodes, we think that copper electrodes might not be suitable to be used for the establishment of rapid electrical kindling. This is because of the changes in kindling parameters, such as increased threshold intensity, retardation of the kindling epileptogenesis, and neuronal loss in the seizure focus. Therefore, the results of such studies can be misleading.

Conclusions

In conclusion, our results confirm that it is possible to establish rapid electrical kindling epileptogenesis in rats with copper electrodes, but due to the neurotoxic effects of copper electrodes, which led to increased threshold intensities, delays in the acquisition of kindled seizures, and tissue damage, we conclude that the use of stainless steel electrodes is preferred even though they are expensive. Therefore, we recommend avoiding the use of copper electrodes for the establishment of the rapid electrical kindling model of epilepsy.

Abbreviations

ADD: After-discharge duration
LTP: Long-term potentiation
NMDA: N-methyl D-aspartate
S4L: Stage four latency
S5D: Stage five duration
SS: Seizure stage

Compliance with ethical guidelines

The animal experiments received the ethics code from the Ethics Committee of University of Isfahan, Isfahan, Iran (Code No. IR.UI.REC.1401.058).

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Not applicable.

Authors' contributions

SB: Conceptualization and funding acquisition. HR, SB, and AY: Investigation, data curation, and formal analysis. HR and SB: Writing—original draft. All authors: Writing—reviewing and editing.

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Conflicts of Interest

The authors report no conflict of interest.

References

1. Devinsky O. Patients with Refractory Seizures. New England Journal of Medicine. 1999;340(20):1565-70. [DOI: 10.1056/NEJM199905203402008] [PMID]
2. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. Experimental Neurology. 1969;25(3):295-330. [DOI: 10.1016/0014-4886(69)90128-9] [PMID]
3. McNamara JO, Byrne MC, Dasheiff RM, Fitz JG. The kindling model of epilepsy: a review. Progress in Neuro-biology. 1980;15(2):139-59. [DOI: 10.1016/0301-0082(80)90006-4]
4. Lothman EW, Perlin JB, Salerno RA. Response properties of rapidly recurring hippocampal seizures in rats. Epilepsy Research. 1988;2(6):356-66. [DOI: 10.1016/0920-1211(88)90047-2]
5. Racine RJ. Modification of seizure activity by electrical stimulation: II. Motor seizure. Electroencephalography and Clinical Neurophysiology. 1972;32(3):281-94. [DOI: 10.1016/0013-4694(72)90177-0]
6. Bulcke F, Dringen R, Scheiber IF. Neurotoxicity of Copper. Advances in Neurobiology. 2017;18:313-43. [DOI: 10.1007/978-3-319-60189-2_16]
7. Heron P, Cousins K, Boyd C, Daya S. Paradoxical effects of copper and manganese on brain mitochondrial function. Life Sciences. 2001;68(14):1575-83. [DOI: 10.1016/S0024-3205(01)00948-1]
8. Szerdahelyi P, Kösa P. Histochemical demonstration of copper in normal rat brain and spinal cord. Histochemistry. 1986;85(4):341-7. [DOI: 10.1007/BF00493487]
9. Borchard S, Bork F, Rieder T, Eberhagen C, Popper B, Lichtmannegger J, et al. The exceptional sensitivity of brain mitochondria to copper. Toxicology in Vitro. 2018;51:11-22. [DOI: 10.1016/j.tiv.2018.04.012]
10. Ristić AJ, Sokić D, Ba čarević V, Spasić S, Vojvodić N, Savić S, et al. Metals and electrolytes in sclerotic hippocampi in patients with drug-resistant mesial temporal lobe epilepsy. Epilepsia. 2014;55(5):e34-e7. [DOI: 10.1111/epi.12593]
11. Beheshti S, Wesal MW. Anticonvulsant activity of the histamine H3 receptor inverse agonist pitolisant in an

electrical kindling model of epilepsy. Neuroscience Letters. 2022;782:136685. [DOI: 10.1016/j.neulet.2022.136685]
12. Beheshti S, Ershadi S, Zamani F, Azimzadeh M, Wesal MW. Differential impact of a ghrelin receptor antagonist or inverse agonist in the electrical kindling model of epilepsy. Epilepsy Research. 2023;197:107234. [DOI: 10.1016/j.eplepsyres.2023.107234]
13. Mirshafiei M, Yazdi A, Beheshti S. Neuroprotective and anti-neuroinflammatory activity of frankincense in bile duct ligation-induced hepatic encephalopathy. Iranian Journal of Basic Medical Sciences. 2023;26(8):966-71. [DOI: 10.22038/IJBMS.2023.68775.14991] [PMID] [PMCID]
14. Cooper R, Crow HJ. Toxic effects of intra-cerebral electrodes. Medical and Biological Engineering. 1966;4(6):575-81. [DOI: 10.1007/BF02474827]
15. Wolske MB, Lian EHC, Leech CK, editors. Kindling Rates in Sprague Dawley Rats as a Function of Copper and Nichrome Electrodes. Proceedings of the Indiana Academy of Science; 1986;96: 453-58. [Link]
16. Blackwood DH, Martin MJ, McQueen JK. Enhanced rate of kindling after prolonged electrode implantation into the amygdala of rats. Journal of Neurosciecne Methods. 1982;5(4):343-8. [DOI: 10.1016/0165-0270(82)90004-8]
17. Luscher W, Wahnschaffe U, Hunack D, Rundfeldt C. Does prolonged implantation of depth electrodes predispose the brain to kindling? Brain Research. 1995;697(1-2):197-204. [DOI: 10.1016/0006-8993(95)00843-F]
18. Babb TL, Kupfer W. Phagocytic and metabolic reactions to chronically implanted metal brain electrodes. Experimantal Neurology. 1984;86(2):171-82. [DOI: 10.1016/0014-4886(84)90179-1]
19. Racine R. Kindling: the first decade. Neurosurgery. 1978;3(2):234-52. [DOI:10.1227/00006123-197809000-00018]
20. D'Ambrosi N, Rossi L. Copper at synapse: Release, binding and modulation of neurotransmission. Neurochemistry International. 2015;90:36-45. [DOI: 10.1016/j.neuint.2015.07.006]
21. Schlief ML, Gitlin JD. Copper homeostasis in the CNS: a novel link between the NMDA receptor and copper homeostasis in the hippocampus. Molecular Neurobiology. 2006;33:81-90. [DOI: 10.1385/MN:33:2:81]
22. Vlachovб V, Zemkovб H, Vyklickэ L, Jr. Copper modulation of NMDA responses in mouse and rat cultured hippocampal neurons. European Journal of Neuroscience. 1996;8(11):2257-64. [DOI: 10.1111/j.1460-9568.1996.tb01189.x]
23. Sharonova IN, Vorobjev VS, Haas HL. High-affinity copper block of GABA(A) receptor-mediated currents in acutely isolated cerebellar Purkinje cells of the rat. European Journal of Neuroscience. 1998;10(2):522-8. [DOI: 10.1046/j.1460-9568.1998.00057.x]
24. Peters C, Mucoz B, Sepьlveda FJ, Urrutia J, Quiroz M, Luza S, et al. Biphasic effects of copper on neurotransmission in rat hippocampal neurons. Journal of Neurochemistry. 2011;119(1):78-88. [DOI: 10.1111/j.1471-4159.2011.07417.x]
25. Marchetti C, Baranowska-Bosiacka I, Gavazzo P. Multiple effects of copper on NMDA receptor currents. Brain Research. 2014;1542:20-31. [DOI: 10.1016/j.brainres.2013.10.029]
26. Liu X, Lin C, Wang S, Yu X, Jia Y, Chen J. Effects of High Levels of Copper on the Depression-Related Memory Disorders. The Journals of Gerontology: Series A. 2022;78(4):611-8. [DOI: 10.1093/gerona/glac222]
27. Baudry M. Long-term potentiation and kindling: similar biochemical mechanisms? Advances in Neurology. 1986;44:401-10. [PMID]
28. Sutula T, Steward O. Facilitation of kindling by prior induction of long-term potentiation in the perforant path. Brain Research. 1987;420(1):109-17. [DOI: 10.1016/0006-8993(87)90245-9]
29. Khajei S, Mirnajafi-Zadeh J, Sheibani V, Ahmadi-Zeidabadi M, Masoumi-Ardakani Y, Rajizadeh MA, et al. Electromagnetic field protects against cognitive and synaptic plasticity impairment induced by electrical kindling in rats. Brain Research Bulletin. 2021;171:75-83. [DOI: 10.1016/j.brainresbull.2021.03.013]
30. Doreulee N, Yanovsky Y, Haas HL. Suppression of long-term potentiation in hippocampal slices by copper. Hippocampus. 1997;7(6):666-9. [DOI: 10.1002/(SICI)1098-1063(1997)7:6<666::AID-HIPO8>3.0.CO;2-C]
31. Salazar-Weber NL, Smith JP. Copper Inhibits NMDA Receptor-Independent LTP and Modulates the Paired-Pulse Ratio after LTP in Mouse Hippocampal Slices. International Journal of Alzheimer's Disease. 2011;2011(1):864753. [DOI: 10.4061/2011/864753]
32. Goldschmith A, Infante C, Leiva J, Motles E, Palestini M. Interference of chronically ingested copper in long-term potentiation (LTP) of rat hippocampus. Brain Research. 2005;1056(2):176-82. [DOI: 10.1016/j.brainres.2005.07.030]
33. Gaier ED, Eipper BA, Mains RE. Pam heterozygous mice reveal essential role for Cu in amygdalar behavioral and synaptic function. Annals of the New York Academy of Sciences. 2014;1314(1):15-23. [DOI:10.1111/nyas.12378] [PMID] [PMCID]