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Implication of long term Nicotine exposure on pain hypersensitivity and cognitomotor functions following repetitive pain stimuli in Wistar rats

Ebifetei Okpe *, Ologhaguo Macstephen Adienbo and Arthur Nwafor Chuemere

Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences University of Port Harcourt, Port Harcourt, Choba, Rivers State, Nigeria.

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Abstract

This study investigates the impact of long-term nicotine exposure on pain hypersensitivity and cognitomotor functions after repeated pain stimuli in Wistar rats. The experimental design consisted of three phases of drug administration: short-term, 14 days; sub-chronic, 35 days; and long-term, 105 days, with treatment groups including nicotine (low: 0.1 mg/kg, high: 0.2 mg/kg), morphine (low: 5 mg/kg, high: 10 mg/kg), and their combination. Pain sensitivity was measured by the tail immersion, analgesy meter, and Randall-Selitto tests, while cognitive and motor functions were measured by the Navigational Maze and Rotarod tests, respectively. Results showed that morphine diminished pain hypersensitivity in a dose-dependent manner but that tolerance developed over time. Nicotine displayed dose-dependent analgesic properties, with higher doses significantly improving pain thresholds and enhancing cognitive performance, especially under conditions of chronic pain. Treatment of combined nicotine and morphine in a synergistic way resulted in better pain relief, improvement of cognitive, and motor functions than with each medicine separately taken. Low-dose nicotine was less effective not only in pain but also in cognitomotor assessment. These findings point to the potency of nicotine, especially in high doses, both as a cognitive enhancer and as an adjuvant to opioids for pain management. The study therefore suggests that a tailored, multi-drug therapeutic approach is in order if the shortcomings of classical analgesics are to be overcome and pain-induced cognitive and motor impairment reduced. Future studies will need to further determine the clinical applicability of these results while taking into account the risks of nicotine addiction.

Keywords: Nicotine; Pain hypersensitivity; Cognition; Motor functions; Morphine

1. Introduction

Nicotine, a potent alkaloid found predominantly in the tobacco plant, exerts profound effects on the central nervous system (CNS). As a psychostimulant, it influences various neurological processes that can lead to both immediate and long-term consequences on mental and physical health [1, 2]. Upon exposure, nicotine is rapidly absorbed into the bloodstream and crosses the blood-brain barrier, where it binds to nicotinic acetylcholine receptors (nAChRs). This interaction triggers the release of several neurotransmitters, most notably dopamine, which plays a crucial role in the brain's reward pathway [3, 4]. The release of dopamine contributes to the feelings of pleasure and reinforcement associated with nicotine consumption, thus fostering addiction. Additionally, the stimulation of nAChRs affects other neurotransmitter systems, including those involving serotonin and norepinephrine, which modulate mood, cognition, and arousal [1, 5]. The acute effects of nicotine are often perceived as beneficial by users, including enhanced attention, decreased appetite, and improved mood [6], These transient effects can lead to an increased likelihood of continued use, perpetuating a cycle of dependency [7,8]. However, chronic nicotine use can result in neuroadaptive changes within the CNS. Over time, the brain becomes reliant on the substance for its neurochemical equilibrium, leading to withdrawal

* Corresponding author: Okpe Ebifetei

symptoms when nicotine levels decline [9, 10]. This highlights nicotine's potential to alter cerebral functioning and contribute to the development of associated psychiatric disorders.

Moreover, nicotine's impact on the CNS extends beyond addiction. Research has demonstrated potential therapeutic applications, particularly in neurodegenerative diseases such as Parkinson's and Alzheimer's [11, 12]. Some studies suggest that nicotine may have neuroprotective effects, possibly aiding in the enhancement of cognitive function and slowing disease progression. Nonetheless, the risks associated with nicotine addiction and the adverse health effects of tobacco use necessitate caution in considering its potential benefits [13].

2. Material and methods

Experimental animals weighing between 80–100g obtained from the animal house of the Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt were used for this study and they were provided with standard laboratory rat feeds and water *ad libitum*. The experimental study design was categorized into three phases: Phase 1 (Short term) where drugs were administered for fourteen days, Phase 2 (sub-chronic study) with a 35-day administration, and Phase 3 (long term) lasting 105 days. The animals were grouped as follows: The experiment was structured into three distinct groups, each subjected to different treatment protocols to evaluate their responses to pain and cognitive tests. Group 1 served as the control group, with subjects in Control 1 administered distilled water and maintained in a stress-free environment throughout the experiment. They were then exposed to cognitomotor tests. In Control 2, subjects were also placed under stress-free conditions but were exposed to various tests without any drug treatment, facilitating a comparison for the effects of other treatments. Group 2, the morphine group, received repetitive pain stimuli through the use of electroconvulsive unit and hot plate and thereafter treated with a low dose of morphine (5 mg/kg) or a high dose (10 mg/kg). Following treatment, subjects were evaluated through various cognitomotor tests. Similarly, Group 3, the Nicotine group, was administered low (0.01 mg/kg) and high (0.2 mg/kg) doses of, with the animals undergoing the same set of pain sensitivity and cognitomotor tests after treatment.

This structured approach allowed for systematic investigation of pain and cognitive responses across different treatments, providing valuable insight into the efficacy of morphine and nicotine in managing pain and pain-induced neurological functions. Neurobehavioral studies were conducted weekly on test groups treated with various substance doses, featuring three trials per week.. Statistical analysis employed one-way ANOVA with Newman-Keuls post-hoc tests to determine significant differences among treatment groups. Ethical approval for the study was granted by the University of Port Harcourt.

In the experimental protocols, we utilized a hot plate from Ugo Basile Srl, set to a pre-determined temperature of 52.5°C, which is suitable for rats [14], to observe responses such as licking, shaking, or stepping of the hindpaws, recording the duration of these responses before removing the rat after a maximum of 60 seconds to prevent skin damage. The tail flick method was employed to assess analgesic activity, where the rat instinctively withdraws its tail from heat, indicating pain perception [15, 17]. The Randall-Selitto test, which evaluates mechanical hyperalgesia, involved applying increasing pressure to the rat's paw or tail until withdrawal or vocalization occurred, using the Ugo Basile Analgesy-Meter [18]. Additionally, the Rotarod test was used to assess coordination and balance in rodents [19], while the climbing/beam walk test evaluated fine motor coordination and balance [20] over three days, with two days for training and one for testing, measuring the time taken to cross a narrow beam and counting paw slips, following protocols from previous studies [21].

3. Results

Table 1 Pattern of Pain response using Tail immersion

GROUPS/TREATMENTS	14 days	% diff	63 days	% diff	105 days	% diff
Group 1 (Control)	1.20±0.37	16.67	2.00±0.00	0.00	4.40b±0.25	-59.09
Group 2 (Pain Only)	1.40±0.25		2.00±0.00		1.80a±1.80	
Group 3 (Pain + 5mg/kg Morphine)	2.20a±0.20	57.14	1.80±0.20	-10.00	2.40a±0.25	33.33
Group 4 (Pain + 10mg/kg Morphine)	2.20a±0.25	57.14	2.20±0.20	10.00	3.60b±0.40	100.00
Group 5 (Pain + 0.1mg/kg Nicotine LD)	2.40ab±0.60	71.43	2.20±0.20	10.00	2.00a±0.00	11.11

Group 6 (Pain + 0.2mg/kg Nicotine HD)	2.60ab±0.40	85.71	2.60ab±0.25	30.00	3.20ab±0.37	77.78
Group 7 (Pain + 5 mg/kg morp5+Nic 0.1)	3.20ab±0.37	128.57	2.40±0.25	20.00	3.60b±0.25	100.00

Values are presented in mean ± sem, n= 5. b Means values are statistically significant (p≤0.05) when compared to the control, a means values are statistically significant (p≤0.05) when compared to Pain Only group.

Table 1 shows the pain response pattern in different experimental groups by using the tail immersion method at three time points: 14 days, 63 days, and 105 days. Group 1 (Control) shows a slight increase in pain response at 14 days (mean 1.20) but a significant drop by 105 days (mean 4.40, -59.09%), suggesting a diminishing response or increasing tolerance to pain over time. In contrast, Group 2 (Pain Only) maintains low and stable pain responses, with a mean of 1.40 and 2.00, respectively, without noticeable change, which indicates consistent pain in an unrelieved state. Group 3 (Pain + 5 mg/kg Morphine) shows a notable increase at 14 days (mean 2.20, +57.14%), but it declines by 63 days to a mean of 1.80 (-10.00%). It therefore suggests a possible development of resistance to morphine. However, at 105 days the response has somewhat recovered to a mean of 2.40. Group 4 (Pain + 10 mg/kg Morphine) represented a consistent rise with high potency, showing that at 105 days, the mean was 3.60 and +100.00%, showing that higher doses maintain pain responses. Group 5 (Pain + 0.1 mg/kg Nicotine LD) shows mild improvement (mean 2.40, +71.43% at 14 days) but less significant effects overall, whereas Group 6 (Pain + 0.2 mg/kg Nicotine HD) exhibits a strong consistent response (mean 2.60, +85.71%) with a peak at 105 days (mean 3.20, +77.78%), suggesting that higher nicotine dosages enhance pain responsiveness. Lastly, Group 7 is Pain + 5 mg/kg Morphine + Nic 0.1, which exhibits the highest response within 14 days of mean 3.20, +128.57%, maintaining its effectiveness by 105 days at a mean of 3.60, +100.00%, showing a synergistic effect of the combined treatments. These findings would indicate that morphine exerts a dose- and time-dependent efficacy, whereas nicotine, on its part, significantly modulates the pain response, reflecting the complexity in the pain management strategy and the development of effective combinations aimed at enhancing analgesia.

Table 2 Pattern of Pain Threshold response using Analgesy Meter

Groups/TREATMENTS	**14 days**	**% diff**	**63 days**	**% diff**	**105 days**	**% diff**
Group 1 (Control)	10.08±1.09	-14.4841	12.28±1.97	19.70684	16.08±2.93	-9.57711
Group 2 (Pain Only)	8.62±0.68		14.70±2.24		14.54±1.63	
Group 3 (Pain + 5mg/kg Morphine)	12.40±2.49	43.85151	10.22±0.87	-30.4762	20.36±1.78	40.02751
Group 4 (Pain + 10mg/kg Morphine)	10.50±3.69	21.80974	11.98±2.62	-18.5034	20.58±1.51	41.54058
Group 5 (Pain + 0.1mg/kgNicotine)	9.28±0.96	7.656613	16.30±3.05	10.88435	18.64±1.63	-26.8226
Group 6 (Pain + 0.2mg/kgNicotine)	18.64ab±2.70	116.2413	18.60±.3.12	26.53061	18.60±3.53	27.92297
Group 7 (Pain +5 mg/kg morph+Nic 0.1mg)	20.76ab±2.62	140.8353	12.28±3.14	-16.4626	16.80±1.39	15.54333

Values are presented in mean ± sem, n= 5. b Means values are statistically significant (p≤0.05) when compared to the control, a means values are statistically significant (p≤0.05) when compared to Pain Only group.

The pain threshold responses for various treatment groups over three time periods, measured using an Analgesy Meter, are presented in Table 2. For Group 1 (Control), the pain threshold mean value at 14 days was 10.08 ± 1.09 with a % difference of -14.48%, while at 63 days it was 12.28 ± 1.97 with an increase of 19.71% and reached 16.08 ± 2.93 by 105 days with a -9.58%. In contrast, Group 2 had a baseline threshold of 8.62 ± 0.68 that rose to 14.70 ± 2.24 at 63 days without showing overall significant changes across the 3 points. Group 3 (Pain + 5 mg/kg Morphine) showed a significant increase to 12.40 ± 2.49 at 14 days (43.85%), then a decrease to 10.22 ± 0.87 at 63 days (-30.48%), and then back to 20.36 ± 1.78 by 105 days (40.03%), indicating that morphine causes a complex response that varies with time. Group 4 Pain + 10 mg/kg morphine shows the same tendency: the improvement at 14 days (10.50 ± 3.69, +21.81%), a further decrease at 63 days (-18.50%), and a prominent rise at 105 days, reaching 20.58 ± 1.51 (+41.54%). Group 5 Pain + 0.1 mg/kg Nicotine started with an average of 9.28 ± 0.96 at 14 days, showing a +7.66% change from baseline; at 63 days, there is some increase: 16.30 ± 3.05, +10.88%, which is drastically reduced by -26.82% at 105 days. Group 6 Pain + 0.2 mg/kg Nicotine - exhibits a significant increase to 18.64 ± 2.70 at 14 days (116.24%), maintains stability at 63 days with 18.60 ± 3.12, and afterwards shows a slight decrease by 105 days to 27.92%. Group 7 represents Pain + 5 mg/kg Morphine + 0.1 mg/kg Nicotine, and the pain threshold was highest at 14 days: 20.76 ± 2.62, +140.84%; then at 63 days, it fell to 12.28 ± 3.14 (-16.46%); and at 105 days, it stabilized at 16.80 ± 1.39. these findings suggest that these treatments had various influences on pain thresholds, showing dramatic fluctuations across time points and conditions. Although the findings do indicate that morphine and nicotine have strong analgesic effect, especially together.

Table 3 Pattern of cognitive response using Navigational maze test

Groups/TREATMENTS	14 days	% diff	63 days	% diff	105 days	% diff
Group 1 (Control)	291.840±8.16	-20.0932	113.20±39.42	76.50177	226.56±21.98	-8.47458
Group 2 (Pain Only)	233.20±9.28		199.80±61.38		207.36±2.02	
Group 3 (Pain + 5mg/kg Morphine)	288.84±8.7	23.85935	277.20a±17.09	38.73874	208.20±0.42	0.405093
Group 4 (Pain + 10mg/kg Morphine)	210.84±7.21	-9.58834	188.04±47.42	-5.88589	208.80±0.42	0.694444
Group 5 (Pain + 0.1mg/kgNicotine LD)	253.68±46.32	8.782161	260.04a±29.89	30.15015	210.60±0.42	1.5625
Group 6 (Pain + 0.2mg/kgNicotine HD)	291.72±8.28	25.09434	300.00a±0.00	50.15015	211.20±0.42	1.851852
Group 7 (Pain + mg/kg morp5+Nic 0.1)	248.52±32.05	6.569468	300.00a±0.00	50.15015	211.80±0.42	2.141204

Values are presented in mean ± sem, n= 5. b Means values are statistically significant (p≤0.05) when compared to the control, a means values are statistically significant (p≤0.05) when compared to Pain Only group.

The following data is from Table 3: the cognitive response by treatment groups over 14, 63, and 105 days via the Navigational Maze Test-the significant negative effects of pain on cognitive performance. In the control group, there was an apparent sharp decline in cognitive performance at 63 days that might have become impaired due to some exterior factor. Similarly, the pain-only group continued to deteriorate in this aspect, bringing out the negative effects of pain. The treatments of morphine were very inconsistent, showing some facilitation at the lower dose of 5 mg/kg compared with pain conditions without morphine, but not at the higher dose of 10 mg/kg. The most surprising finding, however, was the large facilitation produced by nicotine, especially at the higher dose of 0.2 mg/kg, where performance was substantially improved at 63 and 105 days, indicating its potential as a cognitive enhancer under conditions of pain. More interestingly, combination therapies with morphine, caffeine, and nicotine showed that complex approaches can efficiently combat cognitive deficits and thus tailored treatments may be potentially effective in pain and cognitive impairments. Data from Table 3 presents the cognitive responses, as measured by the Navigational Maze Test across treatment groups over 14, 63, and 105 days, showing the great impact of pain on cognitive performance. In the control group, cognitive ability sharply declined at 63 days, indicating possible impairment due to environmental factors. The pain-only group showed consistently diminished performance, underlining the negative effects of pain. Treatments involving morphine exhibited mixed results, with lower doses (5 mg/kg) demonstrating some cognitive enhancement compared to pain alone, while higher doses (10 mg/kg) failed to yield significant improvements. Interestingly, nicotine, particularly at higher doses (0.2 mg/kg), showed substantial benefits, with performance improving notably at both 63 and 105 days, suggesting its potential as a cognitive enhancer in the context of pain. Moreover, groupings of morphine, and nicotine were able to reveal that complex approaches may effectively counteract cognitive deficits, pointing to the potential for tailored treatment strategies in managing pain and cognitive impairments effectively.

Table 4 Pattern of Motor response using Rotarod test

Groups/TREATMENTS	14 days	% diff	63 days	% diff	105 days	% diff
Group 1 (Control)	9.80±2.54	-20.4082	16.00±3.76	-5	16.00±4.12	27.5
Group 2 (Pain Only)	7.80±1.63		15.20±1.28		20.40±3.23	
Group 3 (Pain + 5mg/kg Morphine)	19.00±5.15	143.5897	16.00±3.76	5.263158	20.00±1.41	-1.96078
Group 4 (Pain + 10mg/kg Morphine)	13.00±3.08	66.66667	21.20±4.53	39.47368	9.84±12.18	-51.7647
Group 5 (Pain + 0.1mg/kgNicotine LD)	6.80±1.46	-12.8205	7.40±1.72	-51.3158	10.40±1.72	-49.0196
Group 6 (Pain + 0.2mg/kgNicotine HD)	11.60±3.49	48.71795	6.40±0.51	-57.8947	9.40±0.51	-53.9216
Group 7 (Pain + mg/kg morp5+caff10+Nic0.1)	9.00±1.05	15.38462	22.00±5.30	44.73684	25.00±5.30	22.54902

Values are presented in mean ± sem, n= 5. b Means values are statistically significant (p≤0.05) when compared to the control, a means values are statistically significant (p≤0.05) when compared to Pain Only group.

Table 4 presents the results in summary form for the motor responses from various treatment groups across 14, 63, and 105 days through the Rotarod test, showing different treatments and their influence on motor performance in response to pain. Controls had an initial performance of 9.80 ± 2.54, then had a significant decrease on day 14 and increased again on day 63, demonstrating slight recovery. The pain-only group has the lowest motor function

throughout the time points, starting with 7.80 ± 1.63, which describes how debilitating pain is to the motor skills. On the other hand, Group 3 (Pain + 5 mg/kg Morphine) indicates a significant rise in motor performance, with a percentage increase of 143.59% at 14 days, reflecting the potential of morphine in improving motor performance despite the presence of pain.

Whereas the values in group 3 continued to decline, from day 105 with performance of 20.00 ± 1.41, showing that over time, there would be further considerations toward treatment efficacy. Group 4-Pain + 10 mg/kg Morphine-first shows benefits due to the treatment, 13.00 ± 3.08, dropping considerably at 105 days into the study, at 9.84 ± 12.18, and points toward a high-dosed medication maybe not maintaining the motor functions. Group 5 (Pain + 0.1 mg/kg Nicotine LD) and Group 6 (Pain + 0.2 mg/kg Nicotine HD) showed lower performance at some points, which suggests that at these dosages, nicotine is not very effective. By contrast, Group 7 Pain + 5 mg/kg Morphine + 10 mg/kg Caffeine + 0.1 mg/kg Nicotine shows gradual improvement over time, most dramatic on day 105, and suggests that intervention may facilitate greater motor function even in the presence of pain. Together, these data suggest tremendous variability in the efficacy of the treatments and point to possible benefits of multi-drug interventions against the motor impairments resulting from pain.

4. Discussion

This study examined the effects of chronic nicotine exposure on pain hypersensitivity and cognito-motor functions after repeated pain stimuli in Wistar rats. The study sought to establish the comparative effects of nicotine and morphine on pain management, cognitive function, and motor performance, as well as their possible synergistic benefits. The results are important in elucidating the complex interaction between these treatments and their temporal effects.

4.1. Pain Hypersensitivity and Management

The results indicated clear trends in pain modulation among the treatment groups. Morphine exhibited its typical dose-response relationship, where higher doses, such as 10 mg/kg, consistently enhanced the pain responses in long-term tests, especially in tail immersion and the analgesy-meter. On the other hand, tolerance occurred at lower, repeated doses, that is, 5 mg/kg, with efficacy diminishing over time, demonstrating well-documented morphine pharmacodynamics, wherein the effect of the drug gradually wears off with its prolonged use, resulting in decreased analgesia [22].

Nicotine exhibited a dose-response relationship with respect to its effect on pain hypersensitivity: low doses, like 0.1 mg/kg, had a moderate and inconsistent effect, while high doses of 0.2 mg/kg considerably improved pain thresholds, especially in the early stage at 14 days. Interestingly, the combination of morphine and nicotine (5 mg/kg + 0.1 mg/kg) resulted in a synergistic effect, amplifying pain relief, as evidenced by the substantial improvements in pain response at 14 and 105 days. This synergistic action highlights the potential for combining therapies to enhance pain management, particularly in chronic conditions [23].

4.2. Cognito-motor Functions

The current experiment also examined treatment effects on cognition and motor performance using repeated painful stimulation. Pain itself significantly disrupted the cognitive performance demonstrated in the Navigational Maze Test, consistent with other reports that chronic pain disrupts neural networks involved in cognition [24]. Morphine augmented cognitive performance acutely but did not maintain performance, especially after higher doses 10 mg/kg. This decline may be attributable to the sedative properties of morphine interfering with cognitive processes after a longer duration of time [25].

On the other hand, nicotine proved a very promising substance as a cognitive enhancer at higher doses, such as 0.2 mg/kg. Performance in the maze test obviously improved over time, suggesting that nicotine modulation of nicotinic acetylcholine receptors supports the cognitive resilience in pain-induced stress. This is in agreement with previous research that showed the neuroprotective action of nicotine and improved attention and working memory [26]. The low dose of nicotine (0.1 mg/kg) provided inconsistent enhancements of cognitive functions, which shows that optimum dosage is a crucial factor for therapeutic efficiency.

Motor performance as measured by the Rotarod test also presented similar trends. Pain alone caused significant disruption in motor coordination, while morphine improved performance in a dose-dependent manner before its effects were overcome at higher doses. Nicotine treatment alone conferred only marginal benefits, mainly at lower doses, indicative of a dose-dependent response. Combined administration of morphine, caffeine, and nicotine produced the

most remarkable amelioration in motor performance, especially during the later stages (105 days). These findings suggest that multi-drug regimens may be of benefit in mitigating pain-induced motor deficits [27].

4.3. Implications and Future Directions

The results highlight the potency of nicotine as a therapeutic agent in cognitive and motor impairments associated with chronic pain, especially when combined with other analgesics like morphine. However, long-term risks of nicotine addiction and its adverse health effects cannot be disregarded [28]. Further research is needed to optimize dosing regimens and consider other delivery methods to reduce these risks.

It also points out the weakness of depending on opioids for pain management alone, as their efficacy wears off after a while, with side effects. Integrative approaches, in lower doses, with opioids combined with other adjuvant therapies such as nicotine or other non-addictive agents, may offer a better future for sustainable long-term pain management.

5. Conclusion

The results demonstrate that nicotine has a clear, though at higher doses, significant impact on pain hypersensitivity, cognitive performance, and motor performance. Morphine is potent in managing pain, though with diminishing returns over a longer period of usage. Nicotine added to morphine thus presents a promising avenue for the enhancement of analgesic effects with mitigation of pain-induced deficits in cognition and motor performance. These findings contribute to the emerging evidence of the need for tailored, multi-faceted approaches in the management of chronic pain.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The experimental protocols met the Guidelines for Animal Experimentation and were approved by the ethical Committee of the University of Port Harcourt. This study was conducted in accordance with the National Health Research Ethics Committee (NHREC), 2014.

References

[1] Benowitz N. L. (2009). Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annual review of pharmacology and toxicology, 49, 57–71. https://doi.org/10.1146/annurev.pharmtox.48.113006.094742Pesta, D.H., Angadi, S.S., Burtscher, M. et al. The effects of caffeine, nicotine, ethanol, and tetrahydrocannabinol on exercise performance. Nutr Metab (Lond) 10, 71 (2013). https://doi.org/10.1186/1743-7075-10-71

[2] Jiloha R. C. (2010). Biological basis of tobacco addiction: Implications for smoking-cessation treatment. Indian journal of psychiatry, 52(4), 301–307. https://doi.org/10.4103/0019-5545.74303

[3] Whirl-Carrillo Michelle, Huddart Rachel, Gong Li, Sangkuhl Katrin, Thorn Caroline F, Whaley Ryan and Klein Teri E (2021) An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clinical pharmacology and therapeutics. .bPMID:34216021(opens in new window) DOI:10.1002/cpt.2350

[4] Benowitz N. L. (2009). Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annual review of pharmacology and toxicology, 49, 57–71. https://doi.org/10.1146/annurev.pharmtox.48.113006.094742

[5] Ni, Y. , Li, L. , Qu, Y. , Chen, S. , Zhang, H. and Wang, H. (2022) Advances in the Study of Neural Mechanisms Associated with Exercise to Ameliorate Nicotine Addiction. Advances in Physical Education, 12, 126-141. doi: 10.4236/ape.2022.122010

[6] Martin, L. M., & Sayette, M. A. (2018). A review of the effects of nicotine on social functioning. Experimental and clinical psychopharmacology, 26(5), 425–439. https://doi.org/10.1037/pha0000208

[7] Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D., Telang, F., & Baler, R. (2010). Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. BioEssays : news and reviews in molecular, cellular and developmental biology, 32(9), 748–755. https://doi.org/10.1002/bies.201000042

[8] Becker H. C. (2008). Alcohol dependence, withdrawal, and relapse. Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism, 31(4), 348–361.

[9] Paolini, M., & De Biasi, M. (2011). Mechanistic insights into nicotine withdrawal. Biochemical pharmacology, 82(8), 996–1007. https://doi.org/10.1016/j.bcp.2011.07.075

[10] Jomova, K., Raptova, R., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., & Valko, M. (2023). Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. Archives of Toxicology, 97(10), 2499–2574. https://doi.org/10.1007/s00204-023-03562-9

[11] Brooks, A. C., & Henderson, B. J. (2021). Systematic Review of Nicotine Exposure's Effects on Neural Stem and Progenitor Cells. Brain sciences, 11(2), 172. https://doi.org/10.3390/brainsci11020172

[12] Qian Wang, Weihong Du, Hao Wang, Panpan Geng, Yanyun Sun, Junfang Zhang, Wei Wang, Xinchun Jin,Nicotine's effect on cognition, a friend or foe?,Progress in Neuro-Psychopharmacology and Biological Psychiatry,Volume 124,2023,110723,ISSN 0278-5846,https://doi.org/10.1016/j.pnpbp.2023.110723.

[13] Valentine, G., & Sofuoglu, M. (2018). Cognitive Effects of Nicotine: Recent Progress. Current neuropharmacology, 16(4), 403–414. https://doi.org/10.2174/1570159X15666171103152136

[14] Sara Hestehave, Klas SP. Abelson, Tina Brønnum Pedersen, Gordon Munro. Stress sensitivity and cutaneous sensory thresholds before and after neuropathic injury in various inbred and outbred rat strains, Behavioural Brain Research. 2019;375 (112149)

[15] Bannon AW, Malmberg AB. Models of nociception: hot-plate, tail-flick, and formalin tests in rodents. Current protocols in neuroscience, Chapter. 2007;8. Available:https://doi.org/10.1002/0471142301.ns0809s41

[16] Ommerborn MA, Depprich RA, Schneider C, Giraki M, Franz M, Raab WH, Schäfer R. Pain perception and functional/occlusal parameters in sleep bruxism subjects following a therapeutic intervention. Head & face medicine. 2019;15(1):4.

[17] Available:https://doi.org/10.1186/s13005-019-0188-6

[18] Deuis JR, Dvorakova LS, Vetter I. Methods used to evaluate pain behaviors in rodents. Frontiers in Molecular Neuroscience. 2017;10:284.

[19] Available:https://doi.org/10.3389/fnmol.2017.00284

[20] Randall LO, Selitto JJ. A method for measurement of analgesic activity on inflamed tissue. Archives internationales de pharmacodynamie et de therapie, 1957; 111(4):409–419.

[21] Crawley JN. Behavioural phenotyping of rodents. Comp. Med. 2003;53:140-146.

[22] Southwell AL, Ko J, Patterson PH. Intrabody gene therapy ameliorates motor, cognitive, and neuropathological symptoms in multiple mouse models of Huntington's disease. The Journal of Neuroscience. 2009;29:13589–13602.

[23] Carter RJ, Morton J, Dunnett SB. Motor coordination and balance in rodents; Current Protocols in Neuroscience; 2001.

[24] Ballantyne, J. C., & Mao, J. (2003). Opioid therapy for chronic pain. New England Journal of Medicine, 349(20), 1943-1953. https://doi.org/10.1056/NEJMra025411

[25] Marks, D. M., Shah, M. J., Patkar, A. A., Masand, P. S., Park, G. Y., & Pae, C. U. (2019). Serotonin-norepinephrine reuptake inhibitors for pain control: Premise and promise. Current Neuropharmacology, 7(4), 331-336. https://doi.org/10.2174/157015909789152146

[26] Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., & Gitelman, D. R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. The Journal of Neuroscience, 24(46), 10410-10415. https://doi.org/10.1523/JNEUROSCI.2541-04.2004

[27] Legrain, V., Van Damme, S., Eccleston, C., Davis, K. D., Seminowicz, D. A., & Crombez, G. (2011). A neurocognitive model of attention to pain: Behavioral and neuroimaging evidence. Pain, 152(4), 669-682. https://doi.org/10.1016/j.pain.2010.12.026

[28] Newhouse, P., Singh, A., & Potter, A. (2004). Nicotine and nicotinic receptor involvement in neuropsychiatric disorders. Current Topics in Medicinal Chemistry, 4(3), 267-282. https://doi.org/10.2174/1568026043451615

[29] Benowitz, N. L. (2010). Nicotine addiction. New England Journal of Medicine, 362(24), 2295-2303. https://doi.org/10.1056/NEJMra0809890

[30] Urry, H. L., van Reekum, C. M., Johnstone, T., & Davidson, R. J. (2013). Neural responses to cognitive and emotional challenges during morphine withdrawal. Neuropsychopharmacology, 38(4), 712-720. https://doi.org/10.1038/npp.2012.241