ClinicSearch

Clinical Endocrinology and Metabolism

Muhammad Akbar Malik *

Open Access

Research Article

Unexpected Findings on Agomelatine's Substitutive Effects in Smoking Behavior Reduction

Yang I. Pachankis

Founder, S for Science

*Corresponding Author: Yang I. Pachankis. Founder, S for Science.

Received date: November 16, 2023; Accepted date: November 24, 2023; Published date: November 30, 2023

Citation: Yang I. Pachankis. (2023). Unexpected Findings on Agomelatine's Substitutive Effects in Smoking Behavior Reduction *Clinical Endocrinology and Metabolism*, 2(6) DOI: 10.31579/2641-5194/035.

Abstract

Introduction: The research paper reports the exploratory findings of the clinical trial in attenuating autism spectrum disorder during autoimmune disease intervention.

Methods: Agomelatine is introduced in the trial, and it has been observed that the smoking behavior of the participant was attenuated dose-independent by the medication. Reviews on the comparative mechanisms of actions between nicotine and agomelatine are thus conducted.

Result: The phenomenon may be contributed by agomelatine's substitutive actions through glucose, glycogen, and possibly lipoproteins, and the incompleteness of substitution can be associated with the μ-opioid receptors.

Discussions & Conclusions: The intersection between programmed cell death and epidermal growth factor is an interesting element to be further studied.

Trial registration: The trial is registered on ClinicalTrials.gov with the identifier NCT05930912.

Keywords: amino acids; COVID-19 post-vaccination; ligand-gated ion channels; protein kinase; smoking reduction.

Introduction

The paper reports an unexpected finding from the NCT05930912 trial on agomelatine's smoking behavior reduction effects on a high-functioning autism case. Previous studies on agomelatine, an MT1/MT2 melatonergic receptor agonist and 5-HT2C receptor antagonist that involves indirect norepinephrine release, have established its positive effects on dopamine production *in vivo*, while its psychotropic effects upon mood and anxious states are not yet well-understood in details in terms of endocrinology and metabolism [1-3].

From the positive effects of smoking behavior reduction by agomelatine while treating major depressive disorder (MDD) in the trial, the article is purposed to establish the missing links in the function in order to better understand the neuronal, psychiatric, and endocrine implications between the neuronal nicotinic acetylcholine receptors (nAChRs) and 5-HT_{2C} receptors.

Cognitive-behavioral therapy (CBT) is adopted as the basic principle of the trial. The smoking behavior of the participant, by common sense and intensive medical literature, harmful to health, is taken for an undetermined tendency of the bodily needs not fully satisfied. By literature review, it is found that nicotine, *in vitro*, activates macrophage activities with the side-effect of elevating very LDL without significant cholesterol change, which accelerates atherosclerosis [4]. It was tested in the NCT05711810 trial with the same participant that duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), was effective ameliorating the participant's migraine during the intervention on post COVID-19 vaccination autoimmune pathogen, and the replacement with agomelatine exercised the same function in the immune reflex chain [5]. Moreover, the previous review excluded the possibilities on SARS-CoV-2 Spike 2 protein's infection on macrophages, in comparison with HIV-1 [6].

Methods

I do not presume there is no valid neuropsychological foundations for addictive behaviors, but only that there might be safer and more effective replacements for the foundational factors. In the history of psychiatric medicines, opioids, amphetamine, ketamine, etc. used to be exclusively in the controlled substance lists instead of in the prescription tiers. Discretion, therefore, is exercised in the research design with ample evidence on the necessities. The participant has a heavy smoking history, and a pilot data gathering was conducted for a week from June 20 to 27, 2022 on the psychological elements of smoking reliance behavioral triggering, seen in Table 1.

Emotional Tendency	Summed Intensity	Times Triggered	Cigarettes Smoked	Strategies Used
Negative	-186	40	39	Divert Attention; Recent Happy Memories; Postponation; Emotional Shift
Negative Stimulant	-30	10	9	Work
Negative Supressive	-29	5	5	Stall
Negative Inhibitive	-26	5	5	
Negative Impact	-29	7	7	
Neutral, Mixed & Transitional	-14	19	25	
Positive Suppressive	-7	3	3	
Positive Inhibitive	-12	8	8	
Positive Stimulant	19	5	5	
Positive	41	13	12	Continue Working; No Further Urges
Showing Resilience	-6	19	22	
Deterioration	-96	17	24	
Unspecified	-20	20	30	

Table 1 Emotional feedback of the participant from smoking triggering mechanisms (20 to 27 June, 2022).

The nAChRs, critical in tobacco addiction, are ligand-gated ion channels that are vastly distributed throughout the brain with a key role in synaptic neurotransmission [7]. The mesolimbic dopaminergic system with glutamatergic excitation to midbrain dopaminergic neurons from the ventral tegmental area (VTA) is vital in the behavioral reinforcement [7]. The correlational evidence exists between the participant's autism spectrum disorder (ASD) and potentially physiologically ameliorating effects of activated nAChRs [8].

NICOTINE ACTIONS

NAChRs with physiological ACh-evoked activation and desensitization, apart from indirect involvement with norepinephrine release, are reportedly suspicable of involving rigid body motion of the extracellular domain of each subunit, linked to a global reorganization of the transmembrane domain responsible for ligand-gated ion channels' channel gating [2, 9]. Its precognitive effects are exactly paired with the reported cognitive impairment effects of PPIs [10].

Nicotine excites the prefrontal cortex (PFC) physiology and may contribute positively to curb the attention-deficit/hyperactivity disorder (ADHD) behaviors common in ASD patients [11]. The process is associated with the α7 nAChR - stimulated glutamate release, which stimulates norepinephrine release from the PFC [12, 13]. Circuits in layer III of the dorsolateral PFC that underlie higher cognitive operations are modulated in a unique manner often opposite to classic synapses in sensory cortex, amygdala and hippocampus, and extend to intracellular cyclic adenosine monophosphate (cAMP) signaling events [14]. Furthermore, *in vivo* study with rats suggest α_2-adrenoceptors of the basolateral amygdala (BLA) are involved in nicotine-induced anxiogenic-like behaviors [15].

With analogy to coffee and cola, whereby cola might be more additive than coffee between the two caffeine-rich beverages with the former's sweetness, dopaminergic receptors are suspected to be behind the participant's smoking behaviors. With the polarity of the twenty standard amino acids seen in Figure 1, the *in vivo* study with rats striatum suggested that both presynaptic N-methyl-d-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid / kainate receptors regulating the transmitter release augment monoamine release in cerebral ischemia [16, 17]

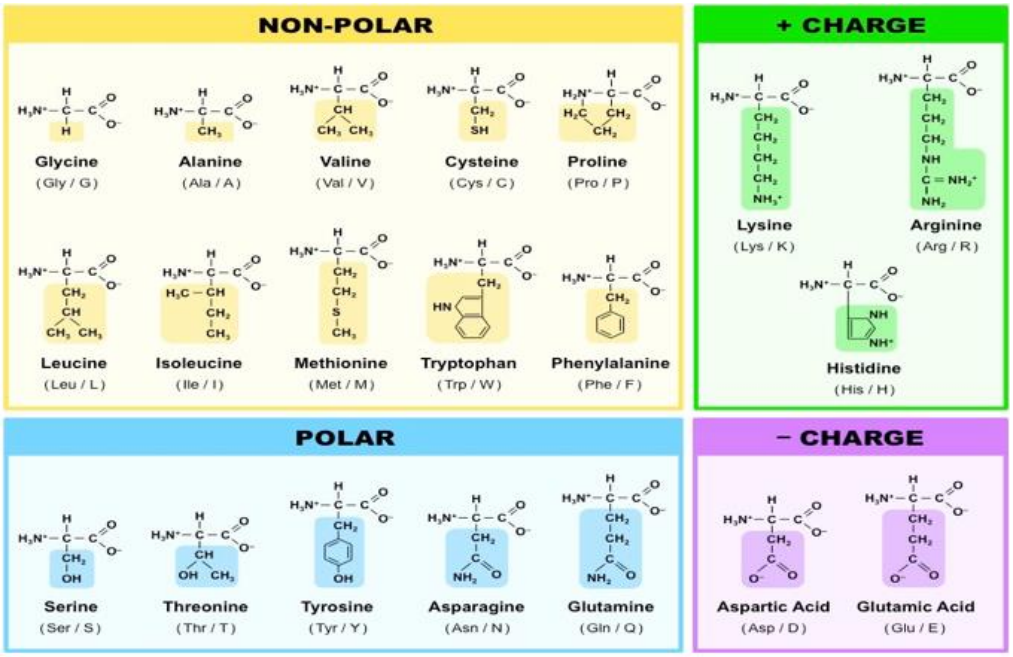

Figure 1 Twenty standard amino acids categorized by physical properties.

Human clinical trials reveal that nicotines also have important actions on the endogenous mu opioid system [18]. From Chart 1 on the intervention and smoking record in the trial, albeit agomelatine contributed positively to the control of smoking behaviors by more than half of the quantities from previous frequencies, no dose-dependent effect has been observed in the trial. No obvious withdrawal symptoms have been observed, and the long-term trend in smoking behavior reduction is documented. The first smoking peak on July 21, 2023 was contributed by social pressure, and the second minor peak on August 5, 2023 seemed to suggest some withdrawal effect from higher to lower dosage. This, hoverer, did not occur in every dosage changes, and further tests and observations are needed for conclusive results [19].

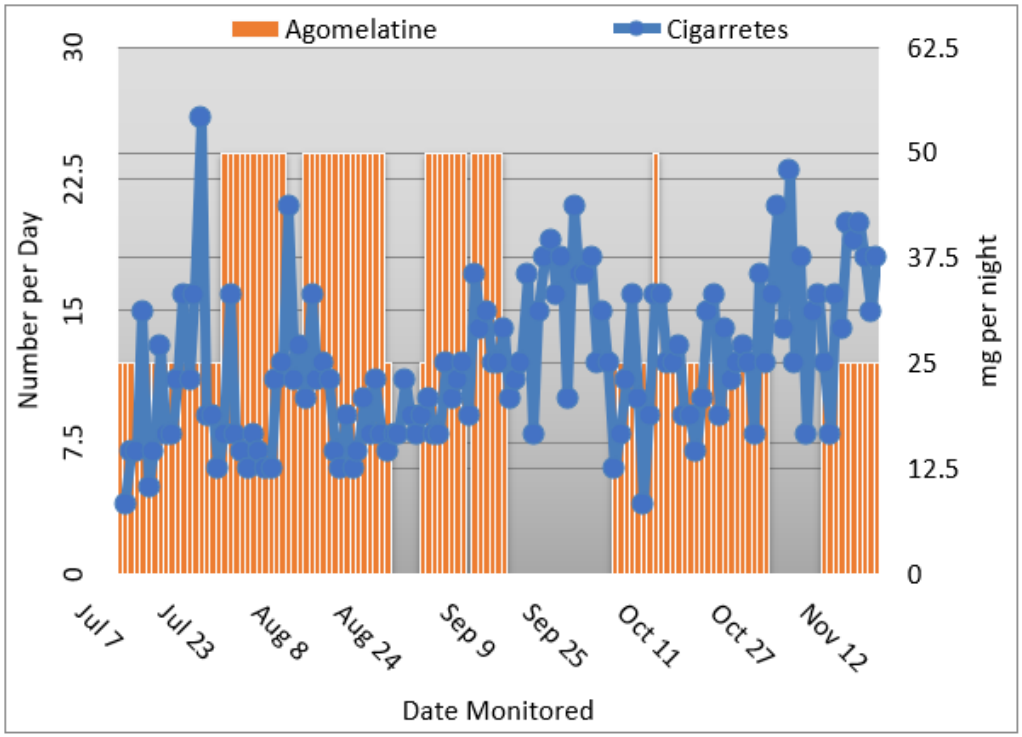

Chart 1 Correlations between agomelatine intervention and cigarette smoking frequencies (July 7 to November 14, 2023).

The observations are attributed to the possibilities on the evidence that nicotine reward is correlated to endogenous opioid signaling in frontal cortex (FC), and [^{11}C]carfentanil binding in FC regions and μ-opioid receptors (MOR) availability in bilateral superior temporal cortices are associated with the actions of nicotines in addiction [20]. Hyper-secretion of non-polar polyaminoacid rich in reactive oxygen species (ROS), such as vasopressin, β-endorphin, etc., from nicotine consumption further raises the questions of the MOR's role in sebaceous immunobiology in the upstream chains and downstream effects [6, 19]. The ROS availability is suspected to be critical in the MOR relevance to [^{11}C]carfentanil [21].

The involvement of the MORs, however, does not imply direct causal relevance for smoking behaviors and addiction. The elevation, through nicotine, of glutamate and dopamine concentrations in the dorsal striatum sensitizes the behaviors *in vivo* with rats [22]. More detailed study observed the boosting effects of norepinephrine on glutamatergic synaptic transmission in the bed nucleus of the stria terminalis (BNST), and the stress-induced reinstatement to drug-seeking is blocked by α_{2A}-adrenergic receptor (AR), with β-AR antagonists enhancing excitatory transmission modulated by norepinephrine [23].

Last but not least, belonging to the "Cys-loop" superfamily of ligand-gated ion channels (LGIC), nAChRs can modulate transmembrane pH values and lipid bilayer interface [9, 24]. Nicotinic receptors of the brain mediate a cationic conductance upon binding agonist; curare, in John Newport Langley's observations, behaves as a competitive antagonist by directly blocking nicotine's antagonist behavior [9]. The cationic permeation of a7-nAChR, a pentameric LGIC (pLGIC), carries a ring of negatively charged residues at position -1' or -2' [9]. The prokaryotic pLGIC acts in the opposite polarity to the eukaryotic anionic glutamate receptor from C. elegans (GluCl), and eukaryotic nAChRs further function in the permeation activities; consequentially, the ring of Glu residues at position -2' by the cytoplasmic entrance to the pore, with two conformations exposed inside and outside the pore [9, 25]. Three lipid molecules per subunit are present in the structure of apo GLIC at 2.9 Å electron density, indicating to the existence of three categories of allosteric binding sites, all located in the upper part of the transmembrane domain [9].

2.1 AGOMELATINE ACTIONS

The pharmacological properties of agomelatine serve as antagonist to the pGLICs MT_1/MT_2 melatonin receptor and 5-HT_{2B}/5-HT_{2C} serotonin receptor [26]. *In vivo* study in combination with gabapentin suggests agomelatine is involved with α_2- and β_2-adrenoreceptor-mediated noradrenergic neurotransmission by actions related to ligated infraorbital nerve [26]. Agomelatine is reported to increase intracellular cAMP, apart from decreasing excessive autophagy and apoptosis of cells in lipopolysaccharides (LPS)-induced depression-like models [3]. The analgesic effects of it through $[Ca^{2+}]i$ signaling are induced to originate from G-protein-coupled receptor activation and phospholipase C (PLC) and protein kinase C (PKC) mediated mechanisms [27, 28].

Contributed by the circumstances of the research, no further cAMP tracing has been adopted to assess the concomitant therapy from the NCT05711810 and NCT05839236 trials targeted in promoting apoptosis, but beta blockers adopted have a possible contribution to the experiment results. The positive correlations between high glucose and ferroptosis, however, have been indirectly observed, with a presumption on the consistency of cell mutational rates, through the cancer antigens (CAs) and carcinoembryonic antigen (CEA) levels seen in Chart 2 [29].

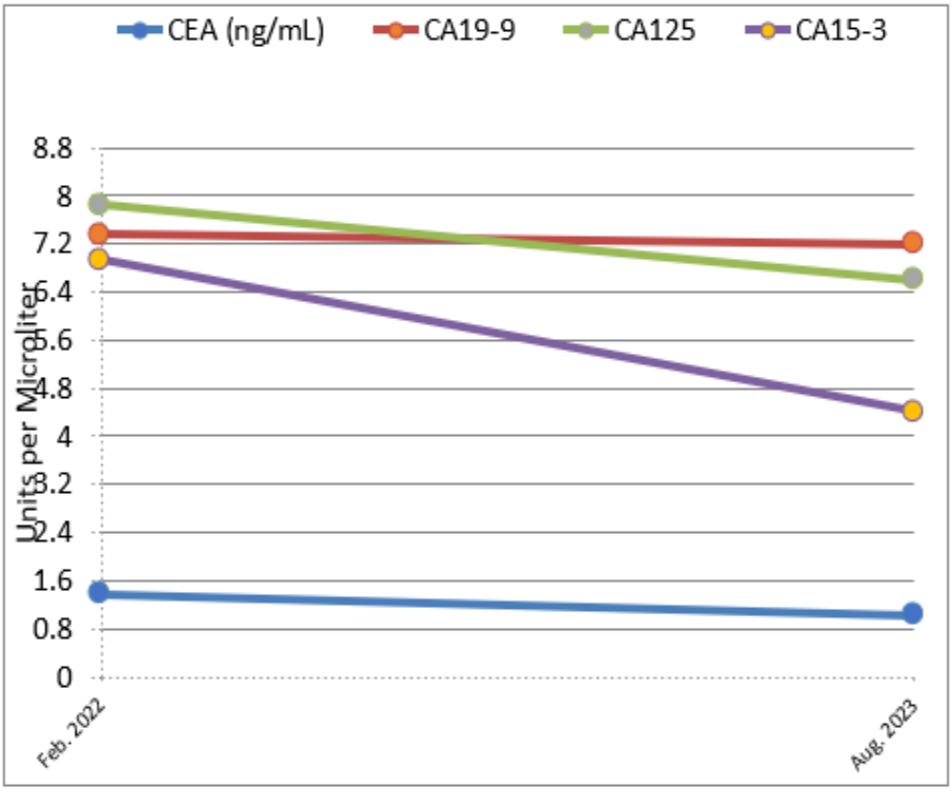

Chart 2 Participant's changes in CAs and CEA sampled from one year apart separated by agomelatine and other interventions.

Contributed by its direct actions on melatonin and daily biophotonic interactions through melanin, agomelatine was found to not increase cAMP-responsive element binding protein phosphorylation, and modulates the time-dependent regulation of mitogen activated protein kinase (MAPK) cascades and Akt/glycogen synthase kinase-3 pathways [30]. Therefore, its functions on limiting smoking behaviors may be contributed by regulating the MAPK-dependent vascular cell migration [31].

Further evidence on brain stems suggests agomelatine may be interventional to mitosis or at least neuronal cell differentiation [32, 33]. Current study has proven agomelatine's interventional effects on endoplasmic reticulum stress and mitochondrial dysfunction through the Ca^{2+} pathway, apart from attenuating ROS production [34]. The regulation effects of agomelatine favors autophagy over apoptosis and impact the rebalancing of short-chain

fatty acids, indicating to its potential mechanism of actions on lipoproteins [35].

Result

The study implies that although nicotines act on cAMP pathways in the PFC, agomelatine's actions in reducing nicotine addiction do not involve the cAMP signaling. The indication narrows the possibilities down to glucose, glycogen, and possibly lipoproteins.

The incompleteness of agomelatine's intervention on smoking behavior is contributed by the MORs. The MORs are associated with nicotine addiction, while no current literature have been discovered associating agomelatine with the MORs.

The two direct results imply that agomelatine's interventional effects on smoking behavior function on the substitution of substances *in vivo*.

Discussions & Conclusions

It was reported that chronic nicotine exposure increases programmed death-ligand 1 (PD-L1) expression in epidermal growth factor receptor (EGFR) mutant cancer cells [36]. There is an intriguing correlation between nicotines and agomelatine with regard to the intricate differences in the similar functional effects in the autophagy and apoptosis pathways.

There is already a closely related cAMP element between agomelatine and nicotine that resembles but are not substitutive; how would that be on the border between programmed and mutational cell deaths?

Funding

No funding is obtained for the research.

Conflict Of Interest

No conflict of interest declared by the author.

Data Availability

The data from the clinical trial can be accessed on Open Science Framework with the DOI: 10.17605/OSF.IO/2MGJK.

References:

1. Guardiola-Lemaitre, B., De Bodinat, C., Delagrange, P., Millan, M.J., Munoz, C., (2014). and Mocaer, E., Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties. *Br J Pharmacol,*. 171(15): p. 3604-3619.
2. Chenaf, C., Chapuy, E., Libert, F., Marchand, F., Courteix, C., et al., (2017). Agomelatine: a new opportunity to reduce neuropathic pain-preclinical evidence. *Pain*, 158(1): p. 149-160.
3. Lan, T.Wu, Y.Zhang, Y.Li, S.Zhu,.et all., (2022). Agomelatine rescues lipopolysaccharide-induced neural injury and depression-like behaviors via suppression of the Gαi-2-PKA-ASK1 signaling pathway. *Journal of Neuroinflammation*, 19(1).
4. Lau, P.P., Li, L., Merched, A.J., Zhang, A.L., et all., (2006). Nicotine Induces Proinflammatory Responses in Macrophages and the Aorta Leading to Acceleration of Atherosclerosis in Low-Density Lipoprotein Receptor −/− Mice. Arteriosclerosis, *Thrombosis, and Vascular Biology*,26(1): p. 143-149.
5. Pachankis, Y.I., (2023). Cardiac Transfer of SARS-CoV-2 Spike Protein Circulation Techniques — Medicine Induced Hemodialysis on "Vaccinated" Immune Attacks. *Biomedical Science and Clinical Research,* 2(1): p. 86-93
6. Pachankis, Y.I., (2023). Plausibility Review on Lipoprotein (A) Infection Path of S2 Autoimmune Pathogen. *Global Journal of Medical Research,* 23(3): p. 5-11.
7. Feduccia, A.A., Chatterjee, S., and Bartlett, S.E., (2012). Neuronal nicotinic acetylcholine receptors: neuroplastic changes underlying alcohol and nicotine addictions. *Front Mol Neurosci*,. 5: p. 83. DOI: 10.3389/fnmol.2012.00083.
8. Pachankis, Y., Adrenaline Intolerance in ASD Curing From Autoimmune Pathogens — Sebaceous Immunobiology in Autoimmune Pathogen Research, in JMIR Preprints. 2023.
9. Corringer, P.J., Le Novere, N., and Changeux, J.P., (2000). Nicotinic receptors at the amino acid level. *Annu Rev Pharmacol Toxicol*,.40: p. 431-458.
10. Goldstein, F.C., Steenland, K., Zhao, L., Wharton, W., Levey, A.I., et all., (2017). Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia. *Journal of the American Geriatrics Society*,. 65(9): p. 1969-1974.
11. Arnsten, A.F., (2010). The use of α-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder. *Expert Rev Neurother*,. 10(10): p. 1595-1605.
12. Russell, V.A. & Wiggins, T.M., (2000). Increased glutamate-stimulated norepinephrine release from prefrontal cortex slices of spontaneously hypertensive rats. *Metab Brain Dis*,15(4): p. 297-304.
13. Ryu, I.S.Kim, J.Seo, S.Y.Yang, J.H.Oh, .et al., (2017). Behavioral changes after nicotine challenge are associated with α7 nicotinic acetylcholine receptor-stimulated glutamate release in the rat dorsal striatum. Scientific Reports,. 7(1).
14. Abdallah, C.G., Averill, L.A., Krystal, J.H., Southwick, S.M., and Arnsten, A.F., (2016). Glutamate and norepinephrine interaction: Relevance to higher cognitive operations and psychopathology. *Behav Brain Sci*,. 39: p. e201.
15. Bashiri, H., Rezayof, A., Sahebgharani, M., Tavangar, S.M., and Zarrindast, M.-R., (2016). Modulatory effects of the basolateral amygdala α 2 -adrenoceptors on nicotine-induced anxiogenic-like behaviours of rats in the elevated plus maze. *Neuropharmacology*, 105: p. 478-486.
16. Ohta, K., Fukuuchi, Y., Shimazu, K., Komatsumoto, S., Ichijo, M., et all., (1994). Presynaptic glutamate receptors facilitate release of norepinephrine and 5-hydroxytryptamine as well as dopamine in the normal and ischemic striatum. *Journal of the Autonomic Nervous System,*. 49: p. 195-202.
17. Humagain, S. (2018). Amino acids: General properties and classification. Online Science Notes; Available
18. Domino, E.F. & Hirasawa-Fujita, M., (2019). Tobacco Smoking and Brain Endogenous Opioid Release: More Than Nicotine Alone. *Nicotine Tob Res*,. 21(6): p. 772-777.
19. Fuxe, K., Andersson, K., Eneroth, P., Härfstrand, A., and Agnati, L.F., (1989). Neuroendocrine actions of nicotine and of exposure to cigarette smoke: *Medical implications. Psychoneuroendocrinology*, 14(1-2): p. 19-41.
20. Kuwabara, H.Heishman, S.J.Brasic, J.R.Contoreggi, C.Cascella,.et al., (2014). Mu Opioid Receptor Binding Correlates with Nicotine Dependence and Reward in Smokers. *PLoS One*, 9(12): p. e113694.
21. Sun, L.Aarnio, R.Herre, E.A.Kärnä, S.Palani, V.et al., (2022). [11C] carfentanil PET imaging for studying the peripheral opioid system in vivo: effect of photoperiod on mu-opioid receptor availability in brown adipose tissue. *European Journal of Nuclear Medicine and Molecular Imaging*, 50(2): p. 266-274.
22. Kim, S., Sohn, S., Ryu, I.S., Yang, J.H., Kim, et all., (2022). Nicotine Rather Than Non-Nicotine Substances in 3R4F WCSC

Increases Behavioral Sensitization and Drug-Taking Behavior in Rats. *Nicotine Tob Res*, 24(8): p. 1201-1207.
23. Egli, R.E., Kash, T.L., Choo, K., Savchenko, V., Matthews, R.T., et all., (2004). Norepinephrine Modulates Glutamatergic Transmission in the Bed Nucleus of the Stria Terminalis. *Neuropsychopharmacology*, 30(4): p. 657-668.
24. Dani, J.A., (2015). Neuronal Nicotinic Acetylcholine Receptor Structure and Function and Response to Nicotine. *Int Rev Neurobiol*, 124: p. 3-19.
25. Cecchini, M. & Changeux, J.-P., (2015).The nicotinic acetylcholine receptor and its prokaryotic homologues: Structure, conformational transitions & allosteric modulation. *Neuropharmacology*, 96: p. 137-149.
26. M'Dahoma, S., Poitevin, M., Dabala, E., Payan, H., Gabriel, C et all., (2018). α2- and β2-Adrenoreceptor-Mediated Efficacy of the Atypical Antidepressant Agomelatine Combined With Gabapentin to Suppress Allodynia in Neuropathic Rats With Ligated Infraorbital or Sciatic Nerve. Frontiers in Pharmacology, 9.
27. Serhatlioglu, I., Bilgin, B., Kacar, E., Ozcan, S., et all., (2019). Agomelatine modulates calcium signaling through protein kinase C and phospholipase C-mediated mechanisms in rat sensory neurons. *J Cell Physiol*,. 234(7): p. 10741-10746.
28. Theivendren, P., Kunjiappan, S., Mariappa Hegde, Y., Vellaichamy, S., Gopal, M., et all., (2021.). Importance of Protein Kinase and Its Inhibitor: A Review, in Protein Kinases - *Promising Targets for Anticancer Drug Research.*
29. Zhao, Y., Shao, G., Liu, X., and Li, Z., (2022). Assessment of the Therapeutic Potential of Melatonin for the Treatment of Osteoporosis Through a Narrative Review of Its Signaling and Preclinical and Clinical Studies. *Front Pharmacol*, 13: p. 866625.
30. Musazzi, L., Seguini, M., Mallei, A., Treccani, G., Pelizzari, M., et all., (2014). Time-dependent activation of MAPK/Erk1/2 and Akt/GSK3 cascades: modulation by agomelatine. BMC Neuroscience, 15(1).
31. Di Luozzo, G., Pradhan, S., Dhadwal, A.K., Chen, A., Ueno, H., et all., (2005). Nicotine induces mitogen-activated protein kinase dependent vascular smooth muscle cell migration. *Atherosclerosis*, 178(2): p. 271-277.
32. Banasr, M., Soumier, A., Hery, M., Mocaër, E., and Daszuta, A., (2006). Agomelatine, a New Antidepressant, Induces Regional Changes in Hippocampal Neurogenesis. *Biological Psychiatry, 59(11): p. 1087-1096.*
33. Dagytė, G., Crescente, I., Postema, F., Seguin, L., Gabriel, C., et all., (2011). Agomelatine reverses the decrease in hippocampal cell survival induced by chronic mild stress. *Behavioural Brain Research*, 218(1): p. 121-128.
34. Chanmanee, T., Wongpun, J., Tocharus, C., Govitrapong, P., and Tocharus, J., (2022). The effects of agomelatine on endoplasmic reticulum stress related to mitochondrial dysfunction in hippocampus of aging rat model. *Chemico-Biological Interactions*, 351.
35. Chen, F., Chen, S., Liu, J., Amin, N., Jin, W., et all., (2021). Agomelatine Softens Depressive-Like Behavior through the Regulation of Autophagy and Apoptosis. *Biomed Res Int*, 2021: p. 6664591.
36. Yeo, C.D., Kim, I.K., Ban, W.H., et all., (2019). Chronic nicotine exposure affects programmed death-ligand 1 expression and sensitivity to epidermal growth factor receptor-tyrosine kinase inhibitor in lung cancer. *Translational Cancer Research*, 8(S4): p. S378-S388.