RESEARCH PAPER

Acta Neurobiol Exp 2023, 83: 194–202
DOI: 10.55782/ane-2023-017

The effect of nicotine on antidepressant and anxiolytic responses induced by citalopram and citicoline in mice

Fatemeh Khakpai[1], Mohammad-Reza Zarrindast[2,3]*

[1] Department of Physiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran,
[2] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran,
[3] Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran,
**Email: zarinmr@ams.ac.ir*

The effect of nicotine on both anxiety and depression has been broadly studied. Moreover, citalopram and citicoline play a role in the modulation of anxiety and depression. This study was designed to examine the effects of nicotine on the antidepressant and anxiolytic responses induced by citalopram and citicoline in mice. Anxiety- and depression-related behaviors were assessed with the elevated plus maze and forced swim test, respectively. The results showed that subcutaneous administration of nicotine decreased open-arm time (OAT) and open-arm entries (OAE) but increased immobility time, suggesting anxiogenic-like and depressive-like effects. Intraperitoneal administration of citalopram increased OAT but decreased immobility time, indicating that citalopram induced anxiolytic-like and antidepressant-like responses. Additionally, an injection of citicoline increased OAE but decreased immobility time, revealing anxiolytic-like and antidepressant-like effects. Interestingly, the subthreshold dose of nicotine potentiated the citalopram and citicoline effects on OAT and immobility time, which revealed anxiolytic-like and antidepressant-like behaviors. Locomotor activity was not significantly changed by any doses of the drugs. In conclusion, these findings suggest that interactions between nicotine and citalopram or citicoline occur upon induction of anxiolytic and antidepressant responses in mice.

Key words: nicotine, citalopram, citicoline, depression, anxiety

INTRODUCTION

Nicotine, as the main component of tobacco, is involved in many processes in both humans and animals, such as anxiety, depression, reward, and addiction (Picciotto et al., 2002; 2015; Andreasen and Redrobe, 2009; Zarrindast and Khakpai, 2019). Nicotine exerts its effect by activating nicotinic acetylcholine receptors (nAChRs), which are highly expressed throughout the brain. These receptors are ligand-gated ion channels and have 12 diverse neuronal nAChR subunits, including α2–α10 and β2–β4 (Zarrindast and Khakpai, 2019). The nAChRs in the nervous system are principally located presynaptically, where they modulate the release of various neurotransmitters, including acetylcholine (ACh), serotonin (5-HT), and norepinephrine (NE) (Kenny et al., 2001). Increased neurotransmitter release, acting at numerous postsynaptic receptors, is the normal mechanism through which nicotine modulates behaviors (Wonnacott, 1997). Of these postsynaptic receptors, the 5-HT receptor plays the primary role in mediating nicotine-induced responses (File et al., 2000; Kenny et al., 2001). Studies have revealed that nicotine administration can increase transcription of the 5-HT1A receptor and increase 5-HT signaling (Kenny et al., 2001; Picciotto et al., 2002). Any interaction between nicotine and the modulation of 5-HT receptor gene expression is of clinical importance, given the key role of these receptors in anxi-

Received 1 July 2022, accepted 14 April 2023

ety and depression (Haddjeri et al., 1998; Heisler et al., 1998; Kenny et al., 2001).

The 5-HT neurons project from the raphe nuclei throughout the brain, where they modulate many functions, e.g., sleep, depression, and anxiety (Silber and Schmitt, 2010; Sprowles et al., 2016). Synaptic concentrations of 5-HT are regulated by the serotonin reuptake transporter (SERT). Selective serotonin reuptake inhibitors (SSRIs), such as citalopram, block the SERT and increase synaptic 5-HT (Sprowles et al., 2016), hence modulating depression and anxiety disorders (Varia et al., 2002; Kokras et al., 2011; Cui et al., 2018; Arias et al., 2019). Citalopram acts as a non-competitive antagonist of several nAChRs. The most compelling evidence that citalopram modulates nAChR activity is based on animal research showing that non-selective (e.g., nicotine) and α7-selective (e.g., PNU-282987) agonists increase the activity of this antidepressant (Popik et al., 2003; Andreasen et al., 2011; Arias et al., 2019).

Moreover, there is an interaction between citalopram and citicoline (cytidine-5'-phosphocholine) in the modulation of anxiety and depression. Research reports indicate that citicoline, in combination with citalopram, increased the effectiveness of SSRI drugs for depression and anxiety treatment (Roohi-Azizi et al., 2017; 2018; Nejati et al., 2020). Several studies revealed that citicoline was an effective therapeutic treatment for managing post-stroke patients suffering from anxiety or anxious-depressive syndrome (Corallo et al., 2020; Arcadi et al., 2021). Citicoline is used in the treatment of neurodegenerative diseases such as ischemia, dementia, and addictive disorders (Adibhatla and Hatcher, 2005; Gruber et al., 2015), and it may induce antidepressant and anxiolytic effects by increasing monoaminergic neurotransmitters (Yoon et al., 2010; Abdolmaleki et al., 2016; Roohi-Azizi et al., 2018). Based on the interactions between nicotine and 5-HT receptors (Kenny et al., 2001), citalopram and nAChRs (Arias et al., 2019), as well as citalopram and citicoline (Roohi-Azizi et al., 2018), we chose to determine whether a subthreshold dose of nicotine has an effect on anxiolytic-like and antidepressant-like responses induced by citalopram and citicoline in mice.

METHODS

Animals

Male NMRI mice (20-25 g) obtained from the Tehran University of Medical Sciences (Tehran, Iran) were used for all experiments and were 6-8 weeks of age at the time of testing. NMRI mice were kept in an animal house with a 12 h light/dark cycle, a controlled temperature of 22 ± 2°C, and 55 ± 10% relative humidity. Mice were housed eight per cage in Plexiglas cages. Food and water were available ad libitum. Experiments were performed between 8:00 a.m. and 2:00 p.m. Each mouse was used only once. All experiments were approved by the Research and Ethics Committee of Tehran University of Medical Sciences. They were carried out according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH publications No. 80-23).

Elevated plus-maze (EPM)

All tests were performed in a dimly lighted room, separated from the colony room. Mice (n=8) were adapted to the test room for 1 h before the experimental test. The EPM apparatus consisted of two open arms (40 × 7) and two closed arms of similar size plus 10 cm-high end and side walls. The arms were linked *via* a central 7 cm × 7 cm area. A mouse was placed in the center of the apparatus with its head facing an open arm and left undisturbed for 300 sec. Then, the mouse was removed and returned to its home cage. The apparatus was cleaned with a 10% chlorine bleach solution between individual test sessions. The mouse was considered to be on the central platform when at least two paws were on it and in an arm whenever all four paws were on it. The time spent in open arms [OAT: (time in open arm/time in open + closed arm)] and the open arm entries [OAE: (number of open arm entries/number of open + closed arm entries)] were used as a measure for anxiety. Moreover, the number of total arm entries was recorded as a measure of spontaneous locomotor activity.

Forced swim test (FST)

Mice (n=8) were individually placed in a beaker (16 cm in diameter) filled with 20 cm water maintained at 24-25°C for 6 min. Great agitation is usually observed during the first 2 min; immobility generally occurs only during the last 4 min and was recorded during this period. The immobility time was defined as when the mouse ceased trying to swim and performed only movements required to keep its head above water.

Drug and animal treatments

The drugs used in the study included nicotine hydrogen tartrate salt (Sigma, St. Louis, CA, USA), cit-

alopram HBR (Daroupakhsh, Tehran, Iran), and citicoline sodium (Minoo, Tehran, Iran). All drugs were dissolved in 0.9% saline except for nicotine, which was dissolved in 0.9% saline with the pH adjusted to 7.2 ± 0.1 with NaOH (0.1 N). Nicotine (0.25, 0.5, and 1 mg/kg) was administered subcutaneously (s.c.) at a volume of 10 ml/kg. Citalopram (1.25, 2.5, 5, and 10 mg/kg) and citicoline (6.25, 12, 25, and 50 mg/kg) were administered intraperitoneally (i.p.) at a volume of 10 ml/kg, 30 min after drug administration. The drug doses were selected based on a pilot study and previous studies (Zarrindast et al., 2012; Nejati et al., 2020). Mice were then subjected to the EPM and then the FST assays. The time interval between the two tests was ten minutes.

Experiment 1

Four groups of mice received saline (10 ml/kg) or nicotine (0.25, 0.5, and 1 mg/kg). Experimental tests were performed 30 min after drug administration. In the experiments, OAT, OAE, locomotor activity, and immobility time were measured as described previously.

Experiment 2

Five groups of mice received saline (10 ml/kg) and different doses of citalopram (1.25, 2.5, 5, and 10 mg/kg) 30 min before tests. The other five groups received nicotine (0.25 mg/kg) and different doses of citalopram (1.25, 2.5, 5, and 10 mg/kg) 30 and 15 min before tests, respectively.

Experiment 3

Five groups of mice received saline (10 ml/kg) and different doses of citicoline (6.25, 12, 25, and 50 mg/kg) 30 min before tests. The other five groups received nicotine (0.25 mg/kg) and different doses of citicoline (6.25, 12, 25, and 50 mg/kg) 30 and 15 min before tests, respectively.

Statistical analysis

The Kolmogorov-Smirnov goodness-of-fit test was used to evaluate the distribution normality and variance homogeneity of data. Data were expressed as mean ± SEM. For data analyses, we used one-way and two-way analyses of variance (ANOVA). Following a significant F-value, *post hoc* analysis was carried out to evaluate specific group comparisons. Differences with $P<0.05$ between experimental groups were considered statistically significant.

RESULTS

The effect of nicotine on anxiety-like and depression-like responses

Fig. 1 shows the effect of nicotine on the EPM and FST. One-way ANOVA and *post hoc* analysis revealed that nicotine at a dose of 1 mg/kg decreased OAT ($F_{(3,28)}=3.892$, $P<0.05$; Fig. 1A) and OAE ($F_{(3,28)}=2.165$, $P<0.05$; Fig. 1B) while increasing immobility time ($F_{(3,28)}=3.093$, $P<0.05$; Fig. 1C). Moreover, the injection of different doses of nicotine had no significant effect on locomotor activity ($F_{(3,28)}=0.583$, $P>0.05$; Fig. 1D), indicating anxiogenic-like and depressive-like responses.

The effect of nicotine on citalopram response in the EPM and FST

Fig. 2 shows the effects of citalopram, in the presence or absence of nicotine, on anxiety- and depression-related phenotypes in the EPM and FST, respectively. Two-way ANOVA revealed a significant interaction between the effects of nicotine (Factor A) and those induced by citalopram (Factor B) on OAT (Factor A: $F_{(1,70)}=27.835$, $P<0.001$; Factor B: $F_{(4,70)}=8.833$, $P<0.001$; Factor (A × B): $F_{(4,70)}=2.618$, $P<0.05$; Fig. 2A) and immobility time (Factor A: $F_{(1,70)}=2.028$, $P>0.05$; Factor B: $F_{(4,70)}=18.106$, $P<0.001$; Factor (A × B); $F_{(4,70)}=2.820$, $P<0.05$; Fig. 2D) but not on OAE (Factor A: $F_{(1,70)}=0.168$, $P>0.05$; Factor B: $F_{(4,70)}=1.622$, $P>0.05$; Factor (A × B): $F_{(4,70)}=0.017$, $P>0.05$; Fig. 2B) and locomotor activity (Factor A: $F_{(1,70)}=1.011$, $P>0.05$; Factor B: $F_{(4,70)}=0.906$, $P>0.05$; Factor (A × B): $F_{(4,70)}=0.217$, $P>0.05$; Fig. 2C). In addition, based on the *post hoc* analysis, citalopram (10 mg/kg) increased OAT ($F_{(4,35)}=3.205$, $P<0.05$) but decreased immobility time ($F_{(4,35)}=4.380$, $P<0.01$) and had no significant effect on OAE ($F_{(4,35)}=0.964$, $P>0.05$) or locomotor activity ($F_{(4,35)}=0.549$, $P>0.05$), indicating that citalopram elicited anxiolytic-like and antidepressant-like responses (Fig. 2, left panels). Moreover, in the presence of a subthreshold dose of nicotine (0.25 mg/kg), citalopram (10 mg/kg) exerted a significant effect on OAT ($F_{(4,35)}=6.745$, $P<0.01$) and immobility time ($F_{(4,35)}=18.238$, $P<0.001$) but not OAE ($F_{(4,35)}=0.734$, $P>0.05$) and locomotor activity ($F_{(4,35)}=0.387$, $P>0.05$) (Fig. 2, right panels). Consequently, the subthreshold dose of nicotine potentiated citalopram's effects on OAT and immobility time, which revealed anxiolytic-like and antidepressant-like responses.

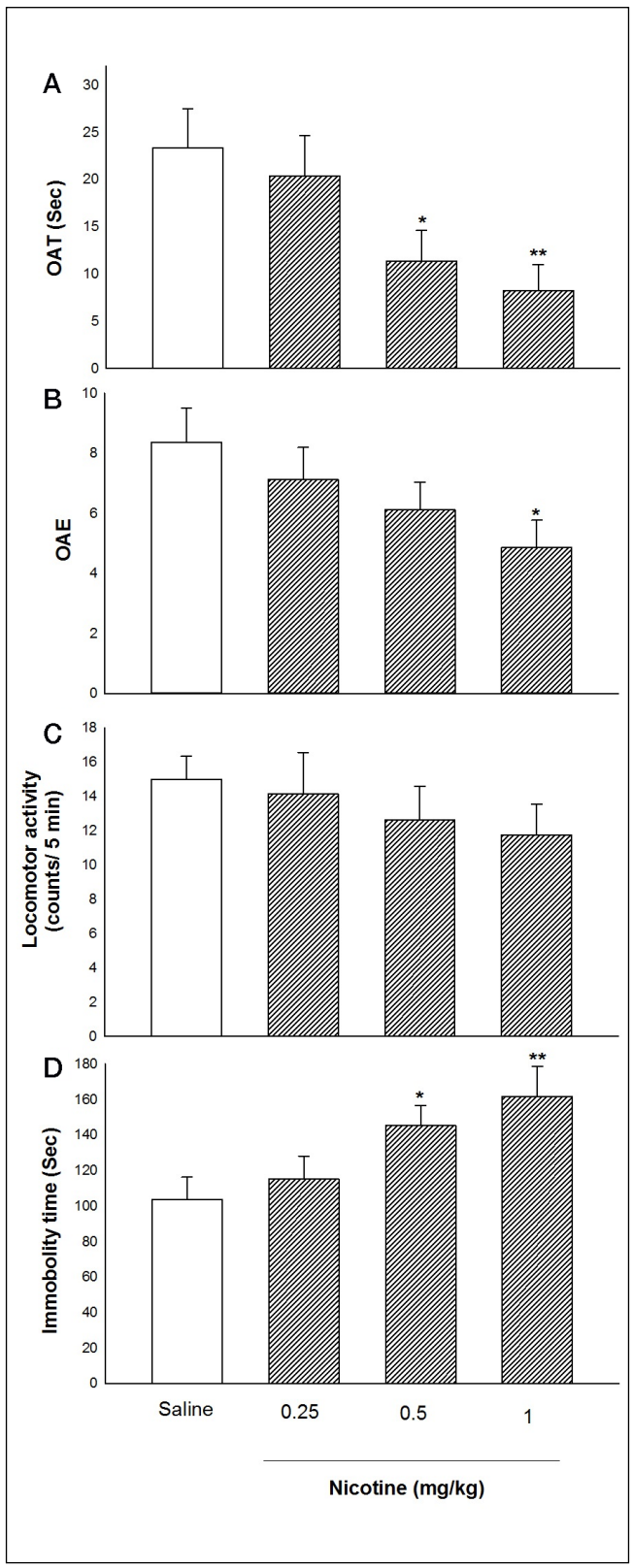

Fig. 1. The effects of various doses of nicotine (0.25, 0.5, and 1 mg/kg) on (A) OAT, (B) OAE, and (C) locomotor activity in the EPM, as well as (D) immobility time in the FST. Data are presented as mean ± S.E.M (n=8). *P<0.05 and **P<0.01 compared to the saline group.

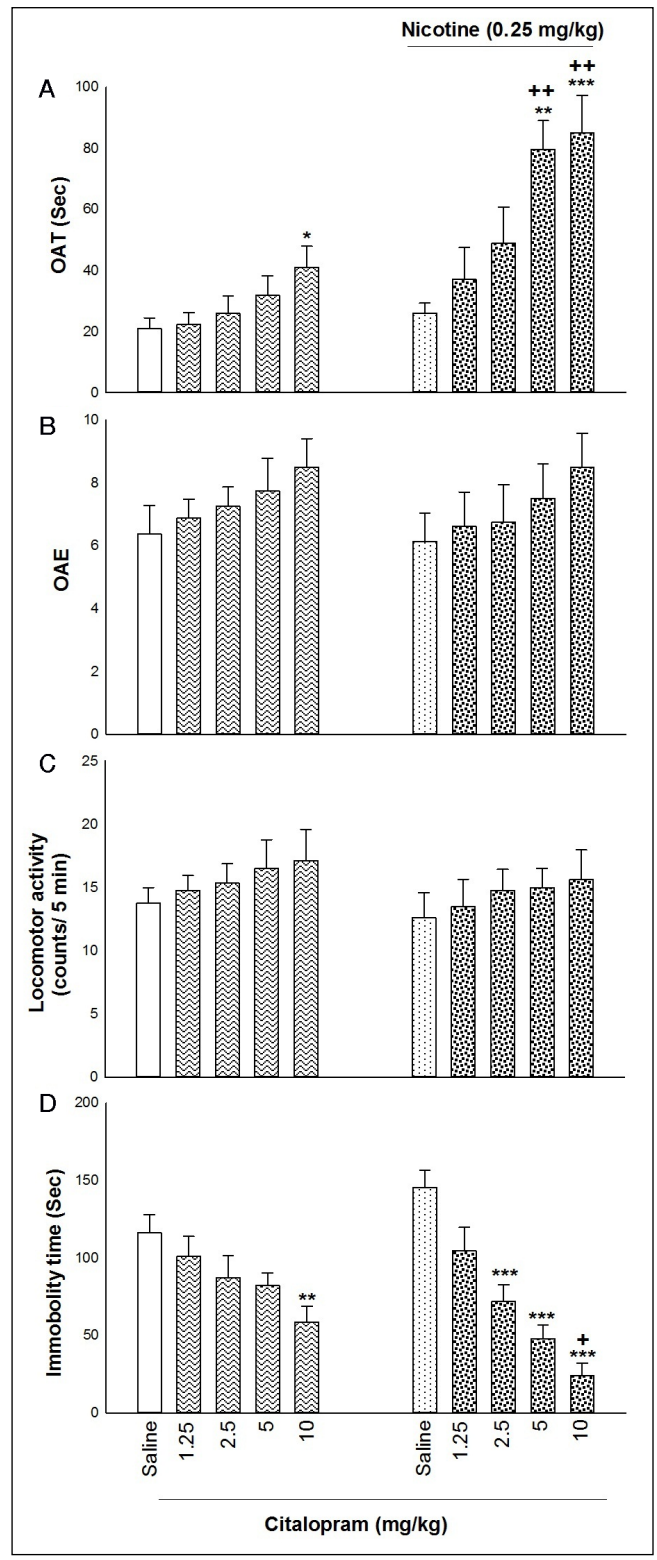

Fig. 2. The effects of nicotine administration alone and co-administration of nicotine with citalopram on (A) OAT, (B) OAE, and (C) locomotor activity in the EPM as well as (D) immobility time in the FST. Data are expressed as mean ± S.E.M (n=8). *P<0.05, **P<0.01 and ***P<0.001 compared to the saline group. $^{+}$P<0.05 and $^{++}$P<0.01 compared to the saline/citalopram group.

The effect of nicotine on citicoline-induced response in the EPM and FST

The effects of citicoline alone or in combination with nicotine on anxiety- and depression-related behaviors are shown in Fig. 3. Two-way ANOVA revealed a clear interaction between nicotine (Factor A) and citicoline (Factor B). This interaction was evident for OAT (Factor A: $F_{(1,70)}$=23.719, P<0.001; Factor B: $F_{(4,70)}$=6.739, P<0.01; Factor (A × B): $F_{(4,70)}$=3.081, P<0.05; Fig. 3A) and immobility time (Factor A: $F_{(1,70)}$=1.227, P>0.05; Factor B: $F_{(4,70)}$=19.240, P<0.001; Factor (A × B): $F_{(4,70)}$=3.271, P<0.05; Fig. 3D) but not for OAE (Factor A: $F_{(1,70)}$=0.065, P>0.05; Factor B: $F_{(4,70)}$=5.923, P<0.001; Factor (A × B): $F_{(4,70)}$=0.173, P>0.05; Fig. 3B) and locomotor activity (Factor A: $F_{(1,70)}$=0.536, P>0.05; Factor B: $F_{(4,70)}$=2.307, P>0.05; Factor (A × B): $F_{(4,70)}$=0.252, P>0.05; Fig. 3C). Further analysis showed that citicoline (50 mg/kg) significantly increased OAE ($F_{(4,35)}$=2.962, P<0.05) but decreased immobility time ($F_{(4,35)}$=3.521, P<0.05) and did not change OAT ($F_{(4,35)}$=1.282, P>0.05) or locomotor activity ($F_{(4,35)}$=0.888, P>0.05) (Fig. 3, left panels). The above result suggested that anxiolytic-like and antidepressant-like effects were induced by citicoline. Furthermore, co-administration of a subthreshold dose of nicotine (0.25 mg/kg) with citicoline (50 mg/kg) resulted in a significant effect on OAT ($F_{(4,35)}$=7.732, P<0.001), OAE ($F_{(4,35)}$=3.101, P<0.05), and immobility time ($F_{(4,35)}$=18.735, P<0.001) but not locomotor activity ($F_{(4,35)}$=1.514, P>0.05) (Fig. 3, right panels). These results show that the subthreshold dose of nicotine potentiated citicoline's anxiolytic-like and antidepressant-like effects.

DISCUSSION

Nicotine has been revealed to affect anxiety and depression in both human and animal studies (Picciotto et al., 2002). Our present results showed that s.c. injection of nicotine (1 mg/kg) reduced OAT and OAE but increased immobility time and had no effect on locomotor activity. This translates to anxiogenic- and depressive-like responses being elicited by nicotine. Several investigations have indicated that nicotine may induce anxiolytic (Brioni et al., 1994), anxiogenic (Ouagazzal et al., 1999a; Cheeta et al., 2001; Olausson et al., 2001), or neutral effects (Balfour et al., 1986; Olausson et al., 1999; Ouagazzal et al., 1999a) on anxiety-like behaviors, which depend on the species, strain, doses, route of administration, experimental model, and number of trials used (Brioni et al., 1993). Some studies have shown that nicotine elicited anxiogenic-like effects at a high dose (1 mg/kg), while

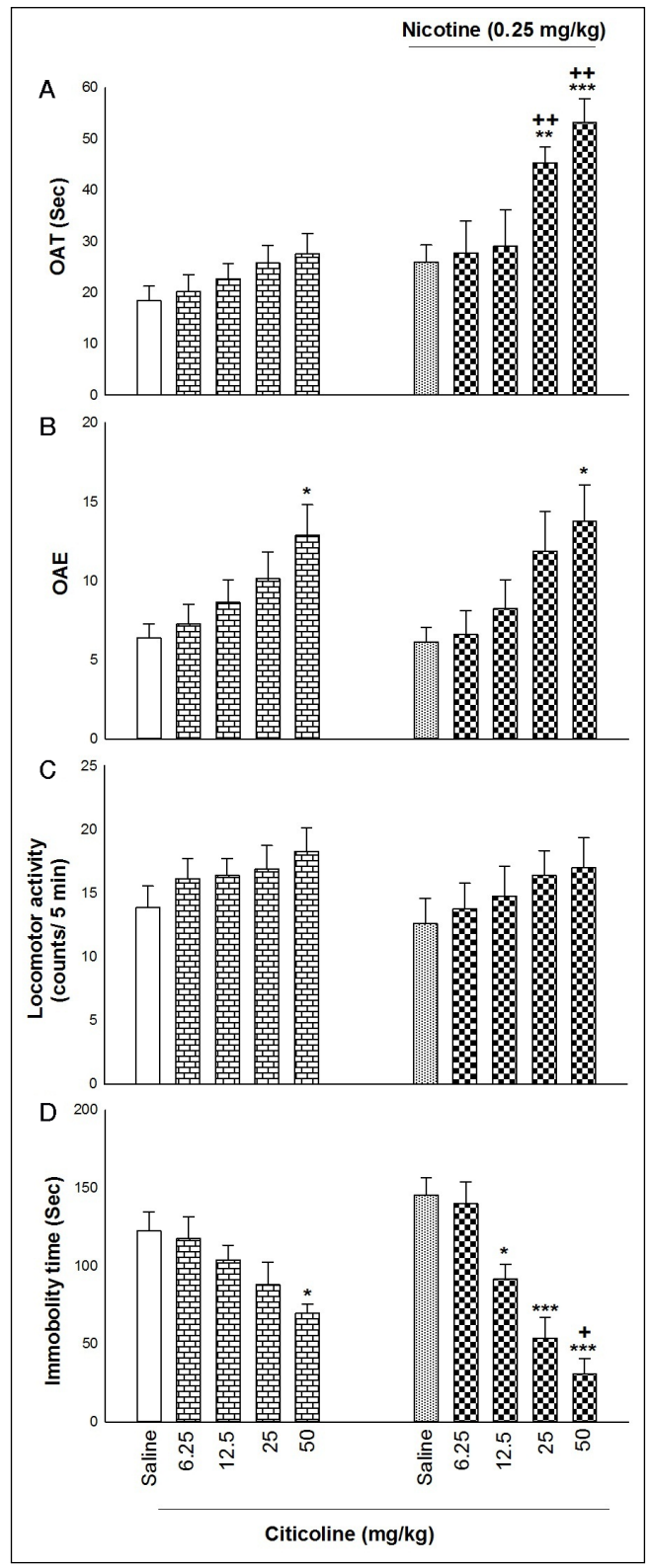

Fig. 3. The effects of nicotine injection alone and co-injection of nicotine with citicoline on (A) OAT, (B) OAE, and (C) locomotor activity in the EPM, as well as (D) immobility time in the FST. Data are expressed as mean ± S.E.M (n=8). *P<0.05, **P<0.01 and ***P<0.001 compared to the saline group. $^{+}$P<0.05 and $^{++}$P<0.01 compared to the saline/citicoline group.

lower doses of the drug (0.01 and 0.1 mg/kg) induced anxiolytic-like responses (Ouagazzal et al., 1999b). The pharmacological effects of nicotine are mediated through the stimulation of nAChRs, promoting the release of ACh, 5-HT, NE, dopamine, glutamate, and GABA, the neurotransmitters involved in anxiety (Piri et al., 2012); hence, we proposed that the anxiogenic-like effect induced by nicotine may be due to the activation of nAChRs, which in turn modulate the release of many neurotransmitters. Furthermore, Nguyen et al. (2021) showed that the anxiogenic effect of nicotine is mediated by the inhibition of dopaminergic neurons projecting to the basolateral amygdala and that this effect involved β2-containing postsynaptic nAChRs in the ventral tegmental area (VTA). Morel et al. (2018) demonstrated that nicotine potentiated a stress-induced depressive response through β2 and α7 nAChRs in the VTA. Similarly, Fernandez et al. (2018) suggested that the cholinergic projection from the laterodorsal tegmentum to the VTA is activated by stress and promotes depression-like behavior. All of these reports highlight the crucial role of dopaminergic signaling in anxiety and depressive behaviors, as shown in many other studies (Chaudhury et al., 2013; Morel et al., 2022).

Also, our findings indicated that injection of nicotine alone induced depressive-like effects by increasing immobility time in the FST. However, co-injection of nicotine and citalopram, as well as nicotine and citicoline, alleviated depression. In mice, nAChRs contribute to the modulation of depression-like responses (Mineur et al., 2018). Furthermore, rodent studies demonstrate that targeting particular nAChR subtypes might provide a therapeutic strategy for treating depression (Mineur et al., 2016). Though no agents acting principally at nAChRs are presently in use for the treatment of depression, it should be noted that numerous current antidepressants, including SSRIs, tricyclics, and bupropion, act as α4β2 nAChR antagonists in cell-based assays (Slemmer et al., 2000; Shytle et al., 2002; Dulawa and Janowsky, 2019). Moreover, nicotine raises serotonergic and noradrenergic neuronal activity and facilitates the release of 5-HT and NE. Previous findings showed that nicotine enhanced the effects of both 5-HT and NE reuptake inhibitors, which suggests an antidepressant action for nicotine (Andreasen and Redrobe, 2009).

Moreover, the results indicated that i.p. injection of citalopram alone or in combination with nicotine enhanced OAT without any significant effect on OAE and locomotor activity but reduced immobility time; citalopram alone or in combination with nicotine-induced anxiolytic-like and antidepressant-like effects. In agreement with our results, several investigations have reported favorable results regarding the use of citalopram in the treatment of depressive and anxiety disorders (Keller, 2000; Baumgartner et al., 2002; Wagner et al., 2004a; 2004b). Citalopram has many potential advantages over other SSRIs, for example, fewer complaints of side effects, mainly initial jitteriness, emotional blunting, and gastrointestinal upset (Keller, 2000; Varia and Rauscher, 2002; Schirman et al., 2010). It also has the highest 5-HT to NE ratio of all SSRIs and a partial weak interaction with the cytochrome-P450 system (Hemeryck and Belpaire, 2002; Lucki and O'Leary, 2004; Schirman et al., 2010).

Citalopram interacts with other compounds, such as nicotine, in the modulation of anxiety and depression (Andreasen and Redrobe, 2009). Moreover, studies have indicated that nicotine administration can increase transcription of 5-HT receptors (Olausson et al., 1999; Kenny et al., 2001; Picciotto et al., 2002). Specifically, nicotine stimulates the release of 5-HT and NE in many forebrain areas (Mitchell, 1993; Kenny et al., 2000; Ma et al., 2005). Nicotine-induced facilitation of 5-HT and NE release may increase or prolong the effects of drugs that inhibit 5-HT and NE transporters. For example, Popik and colleagues (2003) revealed that nicotine and nAChR antagonists potentiate the antidepressant-like effects of citalopram and imipramine. Interestingly, SSRIs such as citalopram interact with nAChRs and inhibit neuronal nAChRs (Arias et al., 2010a; 2010b). Based on animal studies, citalopram modulates nAChR activity so that non-selective (e.g., nicotine) and α7-selective (e.g., PNU-282987) agonists increase the function of this antidepressant (Popik et al., 2003; Andreasen et al., 2011; Arias et al., 2019).

These reports are in agreement with the hyper-cholinergic hypothesis of depression, where cholinergic activity may become exacerbated relative to the noradrenergic system, and a depressive state may develop; therefore, antidepressant-induced nAChR inhibition could contribute to their mechanisms of function (García-Colunga et al., 2016; Arias et al., 2019). Thus, we proposed an interaction between nicotine and citalopram in which the co-administration of a subthreshold dose of nicotine potentiated citalopram's effects on OAT and immobility time, indicating anxiolytic-like and antidepressant-like effects.

Our data also showed that administering citicoline alone or in combination with nicotine elicited anxiolytic-like and antidepressant-like responses. Citicoline is a dietary supplement or drug that may have neuroprotective and cognition-improving effects (Brown and Gabrielson, 2012). It is used to treat neurodegenerative diseases such as bipolar disorder, dementia, stroke, traumatic brain injury, and

addictive disorders. The neuroprotective properties of citicoline may be associated with neuronal membrane phospholipid synthesis and enhancement of several neurotransmitter levels, such as ACh, 5-HT, NE, and dopamine, as well as the improvement of brain tissue markers of oxidative stress (Wignall and Brown, 2014; Roohi-Azizi et al., 2018; Secades and Gareri, 2022). The pharmacological effects of citicoline were found to occur *via* restoring the insertion of membrane enzymes and enhancing their activity (Secades and Gareri, 2022). Citicoline is distributed throughout the body, crosses the blood-brain barrier, and reaches the CNS. Then, it incorporates into the membrane and microsomal phospholipid fraction (Secades and Lorenzo, 2006; Cho and Kim, 2009). Hence, it prevents neuronal phospholipid membrane breakdown and maintains the neuronal membrane after neuronal damage (Cho and Kim, 2009). Interestingly, citicoline exhibits a modulatory role in anxiety and depression behaviors. In agreement with our results, several studies reported that citicoline reduced anxiety-like responses in the open-field test and EPM (Abdolmaleki et al., 2016; Nejati et al., 2020). Citicoline also displayed an antidepressant effect as an adjuvant drug in unipolar and bipolar depression (Roohi-Azizi et al., 2017). As mentioned above, both nicotine and citicoline increased the level of ACh, 5-HT, NE, and dopamine (Piri et al., 2012; Wignall and Brown, 2014; Roohi-Azizi et al., 2018), so we proposed that cross-talk between nicotine and citicoline affected the modulation of anxiety and depression, such that a subthreshold dose of nicotine potentiated the anxiolytic-like and antidepressant-like properties of citicoline.

CONCLUSION

Based on these results, it can be concluded that there are interactions between nicotine and citalopram or citicoline in the production of anxiolytic and antidepressant effects in mice. Nonetheless, more studies are required to clarify the exact mechanisms of action between nicotine, citalopram, and citicoline in the modulation of anxiety and depression.

REFERENCES

Abdolmaleki A, Moghimi A, Ghayour MB, Rassouli MB (2016) Evaluation of neuroprotective, anticonvulsant, sedative and anxiolytic activity of citicoline in rats. Eur J Pharmacol 789: 275–279.

Adibhatla RM, Hatcher JF (2005) Cytidine 5′-diphosphocholine (CDP-choline) in stroke and other CNS disorders. Neurochem Res 30: 15–23.

Andreasen JT, Nielsen EO, Christensen JK, Olsen GM, Peters D, Mirza NR, Redrobe JP (2011) Subtype-selective nicotinic acetylcholine receptor agonists enhance the responsiveness to citalopram and reboxetine in the mouse forced swim test. J Psychopharmacol 25: 1347–1356.

Andreasen JT, Redrobe JP (2009) Nicotine, but not mecamylamine, enhances antidepressant-like effects of citalopram and reboxetine in the mouse forced swim and tail suspension tests. Behav Brain Res 197: 150–156.

Arcadi FA, Corallo F, Torrisi M, Scarfì C, Lo Buono V, Formica C, et al. (2021) Role of citicoline and choline in the treatment of post-stroke depression: an exploratory study. J Int Medical Res 49: 03000605211055036.

Arias HR, Feuerbach D, Bhumireddy P, Ortells MO (2010a) Inhibitory mechanisms and binding site location for serotonin selective reuptake inhibitors on nicotinic acetylcholine receptors. Int J Biochem Cell Biol 42: 712–724.

Arias HR, Feuerbach D, Targowska-Duda KM, Russell M, Jozwiak K (2010b) Interaction of selective serotonin reuptake inhibitors with neuronal nicotinic acetylcholine receptors. Biochemistry 49: 5734–5742.

Arias HR, Jin XT, Gallino S, Peng C, Feuerbach D, Garcia-Colunga J, et al. (2019) Selectivity of (+/-)-citalopram at nicotinic acetylcholine receptors and different inhibitory mechanisms between habenular α3β4* and α9α10 subtypes. Neurochem Int 131: 104552.

Balfour DJ, Graham CA, Vale AL (1986) Studies on the possible role of brain 5-HT systems and adrenocortical activity in behavioural responses to nicotine and diazepam in an elevated X-maze. Psychopharmacology 90: 528–532.

Baumgartner JL, Emslie GJ, Crismon ML (2002) Citalopram in children and adolescents with depression or anxiety. Ann Pharmacother 36: 1692–1697.

Brioni JD, O'Neill AB, Kim DJ, Buckley MJ, Decker MW, Arneric SP (1994) Anxiolytic-like effects of the novel cholinergic channel activator ABT-418. J Pharmacol Exp Ther 271: 353–361.

Brioni JD, O'Neill AB, Kim DJ, Decker MW (1993) Nicotinic receptor agonists exhibit anxiolytic-like effects on the elevated plus-maze test. Eur J Pharmacol 238: 1–8.

Brown ES, Gabrielson B (2012) A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. J Affect Disord 143: 257–260.

Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, Koo JW, et al. (2013) Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature 493: 532–536.

Cheeta S, Irvine E, File SE (2001) Social isolation modifies nicotine's effects in animal tests of anxiety. Br J Pharmacol 132: 1389–1395.

Cho HJ, Kim YJ (2009) Efficacy and safety of oral citicoline in acute ischemic stroke: drug surveillance study in 4,191 cases. Methods Find Exp Clin Pharmacol 31: 171–176.

Corallo F, Scarfì C, Arcadi FA, Formica C, Di Cara M, Palmeri R, et al. (2020) Role of functional pharmacological therapy in post-stroke depression: a narrative review. J Int Medical Res 48: 0300060520950557.

Cui M, Huang CY, Wang F (2018) Efficacy and safety of citalopram for the treatment of poststroke depression: a meta-analysis. J Stroke Cerebrovasc Dis 27: 2905–2918.

Dulawa SC, Janowsky DS (2019) Cholinergic regulation of mood: from basic and clinical studies to emerging therapeutics. Mol Psychiatry 24: 694–709.

Fernandez SP, Broussot L, Marti F, Contesse T, Mouska X, Soiza-Reilly M, et al. (2018) Mesopontine cholinergic inputs to midbrain dopamine neurons drive stress-induced depressive-like behaviors. Nat Commun 9: 4449.

File SE, Cheeta S, Kenny PJ (2000) Neurobiological mechanisms by which nicotine mediates different types of anxiety. Eur J Pharmacol 393: 231–236.

García-Colunga J, Targowska-Duda KM, Arias HR (2016) Functional and structural interactions between selective serotonin reuptake inhibitors and nicotinic acetylcholine receptors. Neurotransmitter 3.

Gruber SA, Sagar KA, Dahlgren MK, Gonenc A, Conn NA, Winer JP, et al. (2015) Citicoline treatment improves measures of impulsivity and task performance in chronic marijuana smokers: a pilot BOLD fMRI study. Int J Neurol Neurother 2: 1–8.

Haddjeri N, Blier P, de Montigny C (1998) Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. J Neurosci 18: 10150–10156.

Heisler LK, Chu HM, Brennan TJ, Danao JA, Bajwa P, Parsons LH, Tecott LH (1998) Elevated anxiety and antidepressant-like responses in serotonin 5-HT1A receptor mutant mice. Proc Natl Acad Sci 95: 15049–15054.

Hemeryck A, Belpaire FM (2002) Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. Curr Drug Metab 3: 13–37.

Keller MB (2000) Citalopram therapy for depression: a review of 10 years of European experience and data from U.S. clinical trials. J Clin Psychiatry 61: 896–908.

Kenny PJ, File SE, Neal MJ (2000) Evidence for a complex influence of nicotinic acetylcholine receptors on hippocampal serotonin release. J Neurochem 75: 2409–2414.

Kenny PJ, File SE, Rattray M (2001) Nicotine regulates 5-HT(1A) receptor gene expression in the cerebral cortex and dorsal hippocampus. Eur J Neurosci 13: 1267–1271.

Kokras N, Sotiropoulos I, Pitychoutis PM, Almeida OF, Papadopoulou-Daifoti Z (2011) Citalopram-mediated anxiolysis and differing neurobiological responses in both sexes of a genetic model of depression. Neuroscience 194: 62–71.

Lucki I, O'Leary OF (2004) Distinguishing roles for norepinephrine and serotonin in the behavioral effects of antidepressant drugs. J Clin Psychiatry 65: 11–24.

Ma Z, Strecker R, McKenna J, Thakkar M, McCarley R, Tao R (2005) Effects on serotonin of (−) nicotine and dimethylphenylpiperazinium in the dorsal raphe and nucleus accumbens of freely behaving rats. Neuroscience 135: 949–958.

Mineur YS, Fote GM, Blakeman S, Cahuzac EL, Newbold SA, Picciotto MR (2016) Multiple nicotinic acetylcholine receptor subtypes in the mouse amygdala regulate affective behaviors and response to social stress. Neuropsychopharmacology 41: 1579–1587.

Mineur YS, Mose TN, Blakeman S, Picciotto MR (2018) Hippocampal alpha7 nicotinic ACh receptors contribute to modulation of depression-like behaviour in C57BL/6J mice. Br J Pharmacol 175: 1903–1914.

Mitchell S (1993) Role of the locus coeruleus in the noradrenergic response to a systemic administration of nicotine. Neuropharmacology 32: 937–949.

Morel C, Fernandez S, Pantouli F, Meye F, Marti F, Tolu, S, et al. (2018) Nicotinic receptors mediate stress-nicotine detrimental interplay via dopamine cells' activity. Mol Psychiatry 23: 1597–1605.

Morel C, Montgomery SE, Li L, Durand-de Cuttoli R, Teichman EM, Juarez B, et al. (2022) Midbrain projection to the basolateral amygdala encodes anxiety-like but not depression-like behaviors. Nat Commun 13: 1532.

Nejati S, Khakpai F, Zarrindast MR (2020) Synergistic effect between citalopram and citicoline on anxiolytic effect in non-sensitized and morphine-sensitized mice: An isobologram analysis. Brain Res 1734: 146701.

Nguyen C, Mondoloni S, Le Borgne T, Centeno I, Come M, Jehl J, et al. (2021) Nicotine inhibits the VTA-to-amygdala dopamine pathway to promote anxiety. Neuron 109: 2604–2615.

Olausson P, Akesson P, Engel JA, Soderpalm B (2001) Effects of 5-HT1A and 5-HT2 receptor agonists on the behavioral and neurochemical consequences of repeated nicotine treatment. Eur J Pharmacol 420: 45–54.

Olausson P, Engel JA, Söderpalm B (1999) Behavioral sensitization to nicotine is associated with behavioral disinhibition; counteraction by citalopram. Psychopharmacology 142: 111–119.

Ouagazzal AM, Kenny PJ, File SE (1999a) Modulation of behaviour on trials 1 and 2 in the elevated plus-maze test of anxiety after systemic and hippocampal administration of nicotine. Psychopharmacology 144: 54–60.

Ouagazzal AM, Kenny PJ, File SE (1999b) Stimulation of nicotinic receptors in the lateral septal nucleus increases anxiety. Eur J Neurosci 11: 3957–3962.

Picciotto MR, Brunzell DH, Caldarone BJ (2002) Effect of nicotine and nicotinic receptors on anxiety and depression. Neuroreport 13: 1097–1106.

Picciotto MR, Lewis AS, van Schalkwyk GI, Mineur YS (2015) Mood and anxiety regulation by nicotinic acetylcholine receptors: A potential pathway to modulate aggression and related behavioral states. Neuropharmacology 96: 235–243.

Piri M, Nasehi M, Shahab Z, Zarrindast MR (2012) The effects of nicotine on nitric oxide induced anxiogenic-like behaviors in the dorsal hippocampus. Neurosci Lett 528: 93–98.

Popik P, Kozela E, Krawczyk M (2003) Nicotine and nicotinic receptor antagonists potentiate the antidepressant-like effects of imipramine and citalopram. Br J Pharmacol 139: 1196–1202.

Roohi-Azizi M, Arabzadeh S, Amidfar M, Salimi S, Zarindast MR, Talaei A, Akhondzadeh S (2017) Citicoline combination therapy for major depressive disorder: a randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol 40: 1–5.

Roohi-Azizi M, Torkaman-Boutorabi A, Akhondzadeh S, Nejatisafa AA, Sadat-Shirazi MS, Zarrindast MR (2018) Influence of citicoline on citalopram-induced antidepressant activity in depressive-like symptoms in male mice. Physiol Behav 195: 151–157.

Schirman S, Kronenberg S, Apter A, Brent D, Melhem N, Pick N, et al. (2010) Effectiveness and tolerability of citalopram for the treatment of depression and anxiety disorders in children and adolescents: an open-label study. J Neural Transm 117: 139–145.

Secades JJ, Gareri P (2022) Citicoline: pharmacological and clinical review, 2022 update. Rev Neurol 75: S1–S89.

Secades JJ, Lorenzo JL (2006) Citicoline: pharmacological and clinical review, 2006 update. Methods Find Exp Clin Pharmacol 28: 1–56.

Shytle RD, Silver AA, Lukas RJ, Newman MB, Sheehan DV, Sanberg PR (2002) Nicotinic acetylcholine receptors as targets for antidepressants. Mol Psychiatry 7: 525–535.

Silber BY, Schmitt JA (2010) Effects of tryptophan loading on human cognition, mood, and sleep. Neurosci Biobehav Rev 34: 387–407.

Slemmer JE, Martin BR, Damaj MI (2000) Bupropion is a nicotinic antagonist. J Pharmacol Exp Ther 295: 321–327.

Sprowles JL, Hufgard JR, Gutierrez A, Bailey RA, Jablonski SA, Williams MT, Vorhees CV (2016) Perinatal exposure to the selective serotonin reuptake inhibitor citalopram alters spatial learning and memory, anxiety, depression, and startle in Sprague-Dawley rats. Int J Dev Neurosci 54: 39–52.

Varia I, Rauscher F (2002) Treatment of generalized anxiety disorder with citalopram. Int Clin Psychopharmacol 17: 103–107.

Varia IM, Cloutier CA, Doraiswamy PM (2002) Treatment of social anxiety disorder with citalopram. Prog Neuropsychopharmacol Biol Psychiatry 26: 205–208.

Wagner KD, Berard R, Stein MB, Wetherhold E, Carpenter DJ, Perera P, et al. (2004a) A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. Arch Gen Psychiatry 61: 1153–1162.

Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE (2004b) A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. Am J Psychiatry 161: 1079–1083.

Wignall ND, Brown ES (2014) Citicoline in addictive disorders: a review of the literature. Am J Drug Alcohol Abuse 40: 262–268.

Wonnacott S (1997) Presynaptic nicotinic ACh receptors. Trends Neurosci 20: 92–98.

Yoon SJ, Lyoo IK, Kim HJ, Kim TS, Sung YH, Kim N, et al. (2010) Neurochemical alterations in methamphetamine-dependent patients treated with cytidine-5'-diphosphate choline: a longitudinal proton magnetic resonance spectroscopy study. Neuropsychopharmacology 35: 1165–1173.

Zarrindast MR, Aghamohammadi-Sereshki A, Rezayof A, Rostami P (2012) Nicotine-induced anxiogenic-like behaviours of rats in the elevated plus-maze: possible role of NMDA receptors of the central amygdala. J Psychopharmacol 26: 555–563.

Zarrindast MR, Khakpai F (2019) The modulatory role of nicotine on cognitive and non-cognitive functions. Brain Res 1710: 92–101.