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Investigation of the Anxiolytic Effects of Calcium Channel-Blocker, Nifedipine, and Beta-Blocker, Propranolol, in Vogel Conflict Rat Model

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Abstract | Anxiety is a common psychiatric disorder, which is widely treated by the addicting substances benzodiazepines. The major objective of the current study is to explore anxiolytic drugs that are devoid of the addicting properties. The cardiovascular drugs, calcium channel-blocker (CCB), nifedipine, and beta-blocker, propranolol, are currently investigated for their possible anxiolytic effects. Anxiolytic properties of CCBs are attributed to inhibition of brain calcium transportation. Propranolol reduces the physical signs of anxiety by blocking adrenergic neurotransmitters. Currently, Vogel conflict paradigm was applied to measure anxiety and validated by using anxiolytic agent, diazepam, and anxiogenic drug, caffeine. Vogel paradigm is based on the conflict between animal's licking water and receiving electric shocks. Rats were individually tested in the anxiometer for a 10-min session; the licks/shock ratio was fixed at 20 licks/1 shock. In addition to the saline-control group, eighty male Wister rats were divided into 10 groups. The animals received one of the treatments, caffeine (10mg/kg), diazepam (0.5mg/kg), nifedipine (2 or 8mg/kg), propranolol (5 or 10mg/kg) and their combinations with caffeine; all treatments were injected intraperitoneal 30 min before testing allowing time for drug absorption. Caffeine treatment could significantly decrease the number of licks and shocks, which reflected an anxiogenic effect. In contrast, treatment with diazepam produced an anxiolytic effect as evident by a significant increase in the number of licks and shocks. The anxiolytic effects of nifedipine and propranolol were evident at the high dose level as measured by increase in licks and shocks.

Keywords: Anxiety, Nifedipine, Propranolol, Caffeine

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INTRODUCTION

Anxiety disorders are among the most frequent mental disorders encountered in clinical practice. Glutamic acid, which is a precursor of GABA, is converted into GABA by the glutamate decarboxylase enzyme. Glutamic acid in corticolimbic circuits interact with GABA, dopamine, serotonin, and other systems involved in the stress response. This indicates their role in the mechanism of anxiety (Nasir *et al.*, 2020). Benzodiazepines are the most commonly used

anxiolytic agents in the treatment of anxiety disorders. The anti-anxiety effect of benzodiazepines is mediated by the GABA-benzodiazepine (BZ) receptor complex, which is functionally and structurally linked to the GABA type A (GABA-A) receptor and a chloride ion channel (Sun *et al*., 2023) where GABA is the principle inhibitory neurotransmitter in the brain (Horvath *et al*., 2020). Although BZs are recognized as the most effective drugs for the treatment of anxiety, their addicting properties and adverse effects have motivated researchers to look for safer drugs.

Benzodiazepines are the major therapeutic group to treat anxiety. However, these compounds have several side effects including physical dependence, tolerance, amnesia, deterioration of cognitive functioning, and psychomotor impairment. Due to the lack of an ideal anxiolytic drug, the search for better anxiolytic drugs continues (Marciniak *et al*., 2004).

Propranolol is a sympatholytic beta blocker; it can pass across the blood brain barrier; therefore, it has effects on the central nervous system, in addition to its peripheral activity (Steenen *et al*., 2016). Besides its ability to block adrenergic receptors, there is also evidence that propranolol may act as a weak antagonist of certain serotonin receptors, 5-HT1A, 5-HT1B, and 5-HT2B. The broad biological activity of propranolol has turned the attention to the possible anxiolytic effects of the drug and may represent a potential alternative treatment for anxiety, which is devoid of the addicting properties of benzodiazepines (Szeleszczuk and Frączkowski, 2022). The availability of oral and intravenous dosage forms of the beta-blocker, propranolol, has prompted experimental studies aimed at investigating the role of the autonomic nervous system in the experience of anxiety. Antianxiety effects of beta-adrenergic receptor blockade have been demonstrated in anxious psychiatric patients after injections of propranolol (Leal *et al*., 2021). Similarly continued oral administration of beta-blocking drugs to the patient has been reported to be effective in reducing symptoms of anxiety (Leal *et al*., 2021). Therefore, propranolol was a good candidate for further research to investigate its potential anxiolytic properties.

The neurotransmitters norepinephrine, serotonin, dopamine, and GABA in the brain, have been implicated in the occurrence of symptoms of anxiety disorders (Catterall, 2011). Voltage-gated calcium channels control the release of neurotransmitters; therefore, it was proposed that calcium channel blockers might inhibit the entry of calcium into the cells, thereby inhibiting its role as an intracellular messenger and producing an anxiolytic effect (Catterall, 2011). Nifedipine, nimodipine and nitrendipine can pass across the blood brain barrier and reach the central nervous system in sufficient amounts to exert central effects (Elliott and Ram, 2011). CCBs are devoid of the side effects seen with traditional anxiolytic drugs like sedation, cognitive impairment and dependence, and thus may represent a potential anxiolytic alternative (Shankpal, 2020).

The characterization of CCBs binding sites in the limbic regions of the brain (Zhang *et al*., 2022) has raised the hope that these drugs might also be useful in the treatment of some central nervous system (CNS) disorders (Pucilowski, 1992). The beneficial effects of verapamil in panic disorder has been recorded by (Goldstein, 1985). These previous results have stimulated the current study to investigate the anxiolytic properties of nifedipine in animal model of anxiety.

Several rodent stress paradigms have been established by researchers; these include foot shock, hypothermia, forced swim, restraint and Vogel conflict test. Vogel conflict test of anxiety is based on conflict situations between reward and punishment: the animal faces two opposing experiences, which creates a state of anxiety (Vogel *et al*., 1971). This animal model is applied for detection of anxiolytic properties of substances (Tang *et al*., 2019). In conflict procedures, animals receive a punishment, e.g., mild electric shock, leading to suppression of a conditioned (learned) response for reinforcement, e.g., food or water (Tang *et al*., 2019). Vogel *et al*. (1971) developed a conflict procedure, in which male rats were water-deprived for 24h and, during a test session of 3 min, drinking was punished by a mild but aversive electric shock delivered via the spout of the bottle every 20 licks. Accordingly, a specific, drug-induced increase in the number of shocks taken (equivalent to water drunk) was considered to reflect anxiolytic properties.

Caffeine produces its actions via antagonism of the adenosine receptor system (Fredholm *et al*., 1999). The adenosine receptor system consists of the four subtypes A1, A2A, A2B and A3, (Fredholm *et al*., 2011). A1 and A2A receptors are implicated in panic disorder (Frick *et al*., 2015). Other neurotransmitters such as glutamate, GABA, acetylcholine, serotonin, and dopamine are regulated by the adenosine A1 and A2A receptors, which have been implicated in anxiety (Durant *et al*., 2010; Frick *et al*., 2016). Further, sleep, arousal, memory and anxiety might be regulated by A1 and A2A receptors (Klevebrant and Frick, 2022). Caffeine consumption has been reported to worsen anxiety (Santos *et al*., 2019; Klevebrant and Frick, 2022). Caffeine has been investigated as an anxiogenic agent in the current model of anxiety. The present study was carried out to investigate the anxiolytic effects of the calcium channel blocker, nifedipine, and beta-blocker, propranolol, in Vogel conflict rat model of anxiety.

MATERIAL AND METHODS

Animals

An eighty-eight male albino Wister rats, obtained from the National Institute of Drug Control and Research, were used in the current study. Animals had an initial body weight 100-130g. They were kept under controlled laboratory conditions, normal light-dark cycle, temperature 25±3 °C to minimize the stress of water deprivation. The animals were housed as pairs of rats per cage to avoid the stress of crowded housing. The animals were water-deprived for 24 hours before running the anxiety test; food was available all the time throughout the study period. All the experiments were performed between 10:00 a.m. and 2:00 p.m. to minimize circadian influences. The experimental work was performed according to the ethical approval number SU-SREC-7-07-23.

Drugs and chemicals

Diazepam, DZP (Valpam® ampoule, Amoun Co. Egypt) with a concentration 5mg/1ml/ampoule, Nifedipine, NFD powder (EIPICO, Egypt) was dissolved in cold saline with the addition of 2 drops of Tween-80; Caffeine, dissolved in normal saline, and Propranolol (Indral® ampoule, AstraZeneca) with a concentration 1mg/1ml/ampoule.

Study design of anxiety

Animals were divided into 11 groups, 8 rats each as follow: Control group: Rats received injections of normal saline (NaCl 0.9%), i.p., this group determined the baseline of anxiety state of the animal via the number of licks and shocks received. Rats were injected with Caffeine, 10mg/kg, i.p., which was considered as a reference anxiogenic agent. Rats were injected with Diazepam 5mg/kg, i.p., which was considered as a standard anxiolytic agent. Rats were injected with Nifedipine at two dose-level (2mg/kg, 8mg/kg, i.p.), rats were injected with Nifedipine 2mg/kg + Caffeine 10mg/kg, i.p., rats were injected with Nifedipine 8mg/kg + Caffeine 10mg/kg, i.p., rats were injected with Propranolol at a two dose-level of (5 mg/kg, 10 mg/kg, i.p.), rats were injected with Propranolol 5mg/kg + Caffeine 10mg/kg, i.p., rats were injected with Propranolol 10mg/kg + Caffeine 10mg/kg, i.p. (Table 1).

Experimental procedures for testing anxiety

The anxiometer, LE 3206 control unit was used to measure anxiety in rats (Figure 1). The shock parameters were set, shock length was 1 second, and shock intensity was 0.3 mAmp. The licks/shock ratio (LSR) was fixed at 20 licks/1 shock; the total trial length (TTL) time was 10 minutes. A shock was supplied each time the LSR is completed, the TTL time started only after the first completion of the LSR. The trial run until the TTL time was completed.

Table 1: Summary of the anxiety experimental design.

Group No.	Treatment Group
1	Control, NaCl 0.9%, i.p.
2	Caffeine 10mg/kg, i.p.
3	Diazepam .5mg/kg, i.p.
4	Nifedipine 2mg/kg, i.p.
5	Nifedipine 8mg/kg, i.p.
6	Nifedipine 2mg/kg + Caffeine 10mg/kg, i.p.
7	Nifedipine 8mg/kg + Caffeine 10mg/kg, i.p.
8	Propranolol 5mg/kg, i.p.
9	Propranolol 10mg/kg, i.p.
10	Propranolol 5mg/kg + Caffeine 10mg/kg, i.p.
11	Propranolol 10mg/kg + Caffeine 10mg/kg, i.p.

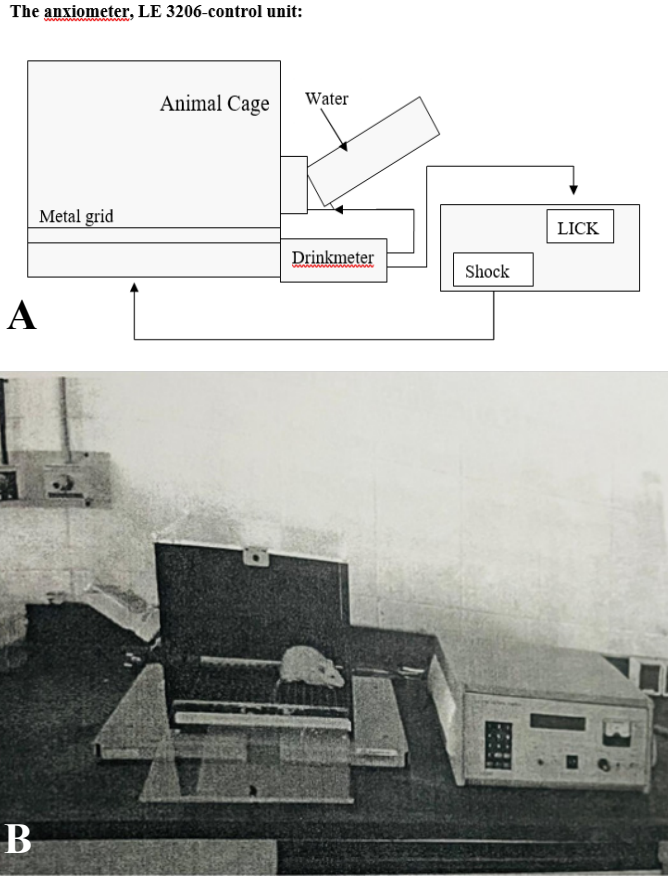

Figure 1: A: Shows a diagrammatic representation of the anxiometer, LE 3206-control unit. B: Photo for the anxiometer during the experiment. The basic paradigm is based on Vogel's test of anxiety (Vogel *et al.*, 1971).

The basic paradigm is based on Vogel's test of anxiety (Vogel *et al.*, 1971). Anxiolytic properties are deduced for drugs which selectively enhance punished responses in the presence of shock. The Vogel conflict test, in which male rats were water-deprived for 48 h and during a test session of 3 min, drinking was punished by a mild but aversive shock delivered via the spout of the bottle every 20 licks. Accordingly, a specific, drug-induced increase in the

number of shocks taken (equivalent to water drunk) was considered to reflect anxiolytic properties. In the present model, the male rats were water-deprived for 24 h and the test duration was 10 min. The electric shock was delivered through the metal grid.

Statistical analysis

Values are expressed as mean±SEM. ANOVA was carried out to determine overall significance among treatment groups. Student t-test was conducted to determine the specific significant difference between each pair of treatment groups. The confidence limit of $p \leq 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The different drug treatments exhibited different effects in the current rat model of anxiety. A summary of the results of the anxiety study is shown in Table 2.

Table 2: A summary of the effects of caffeine (10mg/kg), diazepam (0.5mg/kg), nifedipine (2, 8mg/kg), propranolol (5, 10mg/kg), and the combination of nifedipine or propranolol with caffeine on the number of licks and shocks in a 10-min session of anxiety test of 24-hour water-deprived rats.

Group No.	Anxiety results		
	Treatment group	No. Licks	No. Shocks
1	Control, NaCl 0.9%, i.p.	533±118.8	26±5.9
2	Caffeine 10mg/kg, i.p.	168±14.3*	7.8±0.8*
3	Diazepam .5mg/kg, i.p.	760.6±51.2*	37.8±2.5*
4	Nifedipine 2mg/kg, i.p.	777.4±144.9	38.4±7.3
5	Nifedipine 8mg/kg, i.p.	1134.5±81.3*+	56.5±4.1*+
6	Nifedipine 2mg/kg + Caffeine 10mg/kg, i.p.	669±187*+	34.4±9.3*
7	Nifedipine 8mg/kg + Caffeine 10mg/kg, i.p.	780±145*+	39.4±7.2*
8	Propranolol 5mg/kg, i.p.	450±72.7	22±3.6
9	Propranolol 10mg/kg, i.p.	800.8±69.6*	39.4±3.5*+
10	Propranolol 5mg/kg + Caffeine 10mg/kg, i.p.	193.5±41.9	9.2±2.1
11	Propranolol 10mg/kg + Caffeine 10mg/kg, i.p.	207±42.8	9.8±2.1

Values are expressed as mean±SEM. For all comparisons, differences were considered significant at $p \leq 0.05$.

The anxiogenic effect of caffeine was evident in the present model of anxiety. Caffeine treatment (10mg/kg b.wt.) could significantly decrease the number of licks (Control, 533±118.8 vs. Caffeine, 168±14.3, Figure 2) and cosequently the number of shocks (Control, 26±5.9 vs. Caffeine, 7.8±0.8, Figure 2).

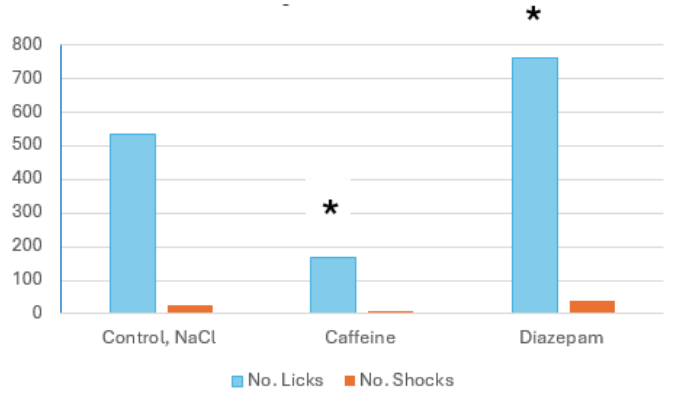

Figure 2: Effects of caffeine (10mg/kg, i.p) and diazepam diazepam (0.5mg/kg, i.p) on the number of licks and shocks/10 minutes session in water-deprived rats. *: Significantly different from control, $p \leq 0.05$.

The traditional anxiolytic agent, diazepam, produced the expected anxiolytic effect in the current animal model of anxiety. Diazepam (0.5mg/kg b.wt.) produced a significant increase in the number of licks in the water-deprived rats (760±51.2, Figure 2) as compared to the control. A corresponding increase in the number of shocks was noted as well (Diazepam, 37.8±2.5, Figure 2). These results proved the validity of the current Vogel conflict test of anxiety.

The calcium channel blocker, nifedipine, showed an anxiolytic effect. Although the number of licks and shocks tended to increase after treatment with nifedipine (2mg/kg b.wt.), the anxiolytic effect of nifedipine was evident at the high dose (Nifedipine, 8mg/kg b.wt.). This high dose produced a significant elevation in the number of licks (1134.5±81.3, Figure 3) and the number of shocks (56.5±4.1, Figure 3) as compared to diazepam in a 10 min session. Therefore, this effect was comparable to the anti-anxiety effect of the standard anxiolytic agent, diazepam.

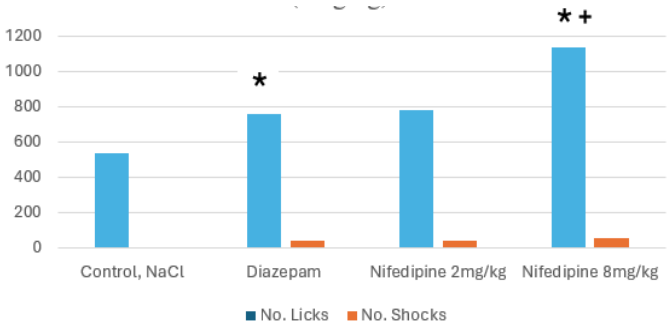

Figure 3: The effect of nifedipine (2 or 8mg/kg, i.p) on the number of licks and shocks/10 minutes session as compared to diazepam (5mg/kg, i.p) in water-deprived rats. *: Significantly different from control, $p \leq 0.05$. +: Significantly different from corresponding treatment (diazepam) $p \leq 0.05$.

Nifedipine treatment (2 and 8mg/kg b.wt.) could successfully reverse the anxiogenic effect of caffeine. The

number of licks and shocks of animals pretreated with caffeine (10mg/kg b.wt.) have significantly elevated after treatment with nifedipine (2 or 8 mg/kg b.wt.); Nifidepine produced a significant increase in the number of licks and the number of shocks in caffeine-pretreated rats (Figure 4). This effect might be due to the central inhibitory effect of nifedipine on calcium transportation, and consequently inhibition of transmitters' release and decrease the excitatory state of the brain.

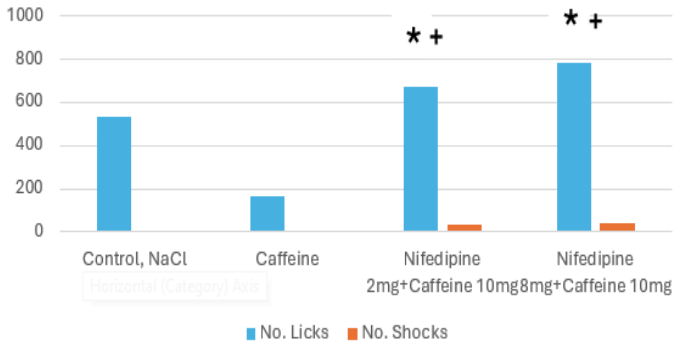

Figure 4: The effect of nifedipine (2 or 8mg/kg, i.p) on the number of licks and shocks/10 minutes session in water-deprived rats pretreated with caffeine (10mg/kg) as compared to caffeine treatment (10mg/kg, i,p). *: Significantly different from control, p≤0.05. +: Significantly different from caffeine, p≤0.05.

The non-selective beta-blocker, propranolol, exhibited some anxiolytic activity in the current animal model of anxiety. This anxiolytic effect was evident only at the high dose level of the drug (Propranolol, 10mg/kg b.wt.). This dose treatment resulted in a significant increase in the number of licks (800.8±69.6) and the number of shocks (39.4±3.5, Figure 5) in the water-deprived rats. This effect was comparable to the anti-anxiety effect of the standard anxiolytic agent, diazepam (Figure 5).

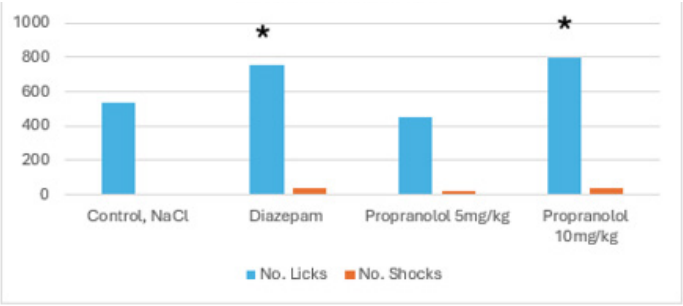

Figure 5: The effect of propranolol (5 or 10mg/kg, i.p) on the number of licks and shocks/10 minutes session in water-deprived rats as compared to diazepam treatment (5mg/kg, i.p). *: Significantly different from control, p≤0.05.

Although the high dose of propranolol (10mg/kg b.wt.) produced an anxiolytic effect in normal rats, it failed to reverse the anxiogenic effect of caffeine in rats pretreated with caffeine; no significant change in the number of licks or the number of shocks was observed after treatment with propranolol in caffeine-pretreated rats (Figure 6). This observation can be partly explained on the basis of the peripheral mechanism of action of propranolol and lack of central effect, which is the site of action of caffeine.

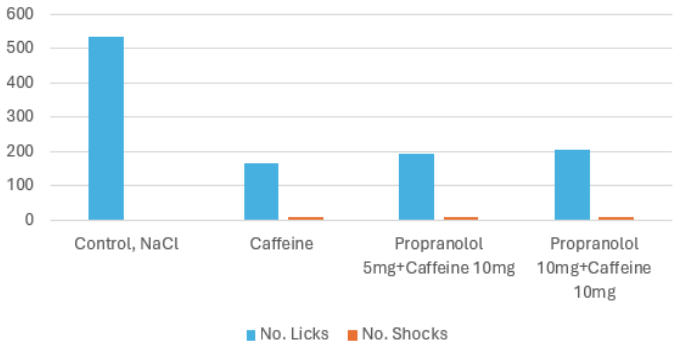

Figure 6: The effect of propranolol (5 or 10mg/kg, i.p) on the number of licks and shocks/10 minutes session in water-deprived rats pretreated with caffeine (10mg/kg).

The Vogel conflict test is a valuable tool in the characterization of both anxiogenic and anxiolytic effects of drugs; this test has the advantage of being an objective, not subjective, method of evaluation of anxiety state in animals. This test of anxiety is based on conflict situations between reward and punishment, which creates a state of anxiety (Vogel *et al.*, 1971). Therefore, because of its objective character, it was used by many researchers to detect both the anxiogenic and anxiolytic properties of substances (Tang *et al.*, 2019). Caffeine consumption has been reported to increase anxiety (Santos *et al.*, 2019; Klevebrant and Frick, 2022). In the current study, Vogel conflict test was used as model of anxiety in rats, where caffeine has been used as an anxiogenic agent. Caffeine was proposed to have several mechanisms of action including the antagonism of adenosine receptors, the release of calcium from intracellular stores, and the antagonism of benzodiazepine receptors (Institute of Medicine Committee on Military Nutrition, 2001).

Therefore, the protective effects of the calcium channel blocker (nifedipine) and the benzodiazepine receptor agonist (diazepam) against anxiety have been investigated in the present study. Caffeine is a stimulant for the central nervous system that can pass across the blood–brain barrier and increase arousal state of the brain. Further, excessive caffeine consumption has been reported to cause symptoms such as anxiety, agitation, and insomnia, (Willson, 2018; Badawoud *et al.*, 2024). Further, anxiety and panic disorder has been reported to increase after consumption of more than six cups of coffee a day (Kendler *et al.*, 2006). In the present study, nifedipine could successfully reverse the anxiogenic effect of caffeine; this effect of nifedipine

could be attributed to its inhibitory effect on calcium mobilization across neuronal membranes and inhibition of neuronal excitability encountered in a state of anxiety.

The evident anxiolytic effect of benzodiazepines in the Vogel conflict test parallels their clinical efficacy in patients (Jee *et al*., 2020). The traditional anxiolytic agent, diazepam, which was used as a reference drug in the present study, produced the expected anxiolytic effect. Diazepam treatment (0.5mg/kg) produced a significant increase in the number of licks in the water-deprived rats. These results may prove the reliability of the current animal model.

Zaidi *et al*. (2020) reported that an effect of β-adrenergic blockers in the relief of post-traumatic stress disorder (PTSD). Giustino and Maren (2015) have proposed that propranolol was effective in reducing fear. Fitzgerald *et al*. (2015) reported similar results. In addition, long-term administration of propranolol effectively reduced elevated norepinephrine (NE) signaling for individuals with chronic PTSD. The present results showed that the non-selective beta-blocker, propranolol, exhibited anxiolytic activity in the current animal model of anxiety. This anxiolytic effect was evident only at the high dose level of the drug (Propranolol, 10mg/kg). This dose treatment resulted in a significant increase in the number of licks and shocks in the water-deprived rats.

Beta-blockers have been shown to decrease aggressive behavior in animals after both acute and chronic administration. All beta-blockers enter the CNS in pharmacologically sufficient concentrations. Leavitt *et al*. (1989) reported that nadolol caused a significant decrease in aggression in 6-hydroxydopamine-treated rats. Two hypotheses have been proposed to explain the mechanism of anxiolytic action of propranolol: (Srinivasan, 2019) Propranolol may reduce peripheral beta-adrenergic neural transmission and, hence, the afferent feedback from the peripheral nervous system. This reduction of peripheral afferent message to the central nervous system may decrease the mechanism of maintenance of anxiety levels (Steenen *et al*., 2016). The beta-blockers may have a direct effect on the central nervous system, as well as the peripheral nervous system, and this central effect primarily accounts for the decrease in the basal anxiety level. These proposed mechanisms of action maybe partially explain the present observed anti-anxiety effect of the beta-blocker, propranolol, in caffeine-untreated animals, meanwhile, propranolol failed to reverse the anxiety observed in caffeine-pretreated rats.

Patients with anxiety may evoke mental images of anxious situations and bring on signs of peripheral autonomic activation, such as tachycardia, decreased blood flow to the fingers, and lowering of skin temperature. Adrenaline, noradrenaline, which act as neurotransmitters across synapses in the brain, are involved as chemical mediators in the fear response (Attia *et al*., 2024). Various anxiolytic agents, e.g., tranquilizers and sedative-hypnotics, may reduce the functional catecholamines at the synaptic level. Presumably, beta adrenergic blockers, which can pass through the blood-brain barrier, are capable of reducing the level of catecholamines in the adrenergic pathways of the brain so that anxiety levels would be decreased (Leavitt *et al*., 1989).

Naderi *et al*. (2019) have reported that calcium channel blockers (CCBs) might have anxiolytic effects, the inhibitors of L- (nifedipine) and T-type (amiloride) calcium channels and endoplasmic reticulum Ca2+-ATPase induced anti-anxiety effect. In the current study, the calcium channel blocker, nifedipine, showed anxiolytic activity. Although the number of licks and shocks tended to increase after treatment with nifedipine (2mg/kg), the anxiolytic effect of nifedipine was evident at the high dose (Nifedipine, 8mg/kg). The later dose produced a significant elevation in the number of licks and shocks in a 10 min session.

The clinical and experimental evidence for anxiolytic effects of CCBs is limited and variable with the test procedures as well as with different classes of CCBs. Ethanol and benzodiazepine withdrawal induced activity deficit in the plus maze was reduced following treatment with verapamil, diltiazem and nicardipine (Little, 1991). Nitrendipine was ineffective against ethanol withdrawal induced anxiety (File *et al*., 1992). These variable reports and the heterogenicity of CCAs, both chemically and functionally, prompted the present study to investigate and compare the anxiolytic-like effects of nifedipine. Benzodiazepines showed a strong anxiolytic profile (Green, 1991). Hence, diazepam was used as positive control to compare the results of the currently tested drugs.

Foitzick *et al*. (2020) reported that activation of GABA-A receptors by positive allosteric modulators, such as benzodiazepines, barbiturates and ethanol, induced adaptive changes that result in tolerance. Neuronal activity modulates the strength of GABAergic transmission by a mechanism that involve the influx of calcium through L-type voltage-gated calcium channels (L-VGCC) (Uusi-Oukari and Korpi, 2010). Prolonged exposure to GABA-A receptor allosteric modulators regulates L-VGCC; in particular, benzodiazepine treatment potentiated calcium currents through L-VGCC in rat hippocampal neurons (Xiang *et al*., 2008). In addition, it was reported that benzodiazepine-induced disruption of GABAergic synapses is mediated by calcium mobilization from intracellular compartments (Nicholson *et al*., 2018; Ma and Zhang, 2022) showed that nifedipine in patients effectively improved adverse emotions such as depression and anxiety

and promoted disease recovery. It is concluded that both nifedipine and propranolol showed anxiolytic effects in the current animal model of anxiety; further clinical research is recommended to establish a possible clinical benefit of these drugs and their specific mechanisms in the treatment of anxiety disorders; these drugs may replace the currently used anxiolytics, mainly benzodiazepines, and avoid their addicting adverse effects.

CONCLUSIONS AND RECOMMENDATIONS

In the current experimental study, the rat model of anxiety has been validated, caffeine treatment proved an anxiogenic effect, whereas the anxiolytic effect of diazepam treatment was evident. Treatment with either nifedipine or propranolol at high dose levels exhibited anxiolytic effects. Further clinical studies are recommended to explore the repositioning of these drugs as anxiolytic agents, which are devoid of the addicting properties of the traditional anxiolytics, benzodiazepines.

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NOVELTY STATEMENT

The present research work provided the evidence of anxiolytic properties for the cardiovascular drugs, nifedipine (calcium channel blocker), and propranolol (beta-blocker). Further, the site of action of these drugs as anxiolytics was clarified via assessing the ability of the drug to reverse the central anxiogenic effect of caffeine. These non-addicting drugs may represent alternative anxiolytic agents to the traditional addicting anxiolytics, benzodiazepines.

AUTHOR'S CONTRIBUTION

EW: Conceptualization, writing original draft, funding acquisition, writing original draft, editing. TMI: Conceptualization, writing review, editing, formal analysis, project administration. MEEA: Data curation, resources, methodology, writing original draft, editing, formal analysis.

Ethical approval

The research was conducted in accordance with the ethical standards set forth in Sinai University- Arish Campus and approved from the Scientific Research Ethics Committee under number SU-SREC-7-07-23 dated 07/2023.

Conflict of interest

The authors have declared no conflict of interests regarding the publication of this article.

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