1: Regul Toxicol Pharmacol. 2005 Mar;41(2):122-7. Epub 2004 Dec 19.

NAN-190, a possible specific antagonist for methamphetamine.

Ginawi OT, **Al-Majed AA**, **Al-Suwailem AK**.

Department of Pharmacology, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia. otginawi@hotmail.com

Effect of NAN-190, a selective 5-HT(1A) receptor antagonist, on methamphetamine-induced locomotor activity, anorexia, analgesia, and hyperthermia was investigated in male mice. Methamphetamine (1.5 mg/kg, i.p) produced a significant increase in locomotor activity, which was significantly antagonized by NAN-190 at a dose of 4 mg/kg, i.p. NAN-190 did not alter the antinociceptive activity of mice when it was administered alone. Methamphetamine (2 mg/kg, i.p) produced a significant decrease in food intake of mice, which were deprived of food during the previous 24h. This anorectic activity of methamphetamine was significantly antagonized by NAN-190 at a dose of 2 mg/kg, i.p. NAN-190 did not alter the food intake of mice when it was administered alone. Methamphetamine (2 mg/kg, i.p) also produced a significant increase in body temperature of mice, which was significantly antagonized by NAN-190 at a dose of 0.5 mg/kg, i.p. NAN-190 did not alter the body temperature of mice when it was administered alone. In the writhing test, methamphetamine (1 mg/kg, i.p) produced a significant antinociceptive effect in mice. This was significantly antagonized by NAN-190 at a dose of 1 mg/kg, i.p. NAN-190 did not alter the antinociceptive activity of mice when it was administered alone. The results of the present study indicate a possible role for serotonergic mechanisms, in addition to the catecholaminergic systems, in the above-studied activities of methamphetamine in mice. This role is possibly mediated through direct stimulation of the 5-HT(1A) receptor subtype. All of the above-studied activities of methamphetamine were antagonized by NAN-190, which may indicate that NAN-190 is a possible antagonist for methamphetamine.

PMID: 15698535 [PubMed - indexed for MEDLINE]

2: Pharmacol Res. 2005 Mar;51(3):255-9.

Ondansetron, a selective 5-HT3 antagonist, antagonizes methamphetamine-induced anorexia in mice.

Ginawi OT, **Al-Majed AA**, **Al-Suwailem AK**.

Department of Pharmacology, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia. otginawi@hotmail.com

Effects of some selective serotonergic (5-HT) antagonists on methamphetamine-induced anorexia were investigated in male mice. The least possible dose of methamphetamine alone that caused significant anorectic activity was 11 micromolkg(-1), i.p. (2 mgkg(-1)). Various doses of some selective serotonergic receptor antagonists were administered half an hour before the above mentioned dose of methamphetamine. Methiothepin potentiated, whereas NAN-190, methysergide, mianserin and ondansetron antagonized methamphetamine-induced anorectic activity. The least possible doses of these antagonists which modified methamphetamine-induced anorexia were as follows: methiothepin (1.1 micromolkg(-1), i.p.), NAN-190 (4.2 micromolkg(-1), i.p.), methysergide (2.1 micromolkg(-1), i.p.), mianserin (3.3 micromolkg(-1), i.p.) and ondansetron (0.003 micromolkg(-1), i.p.). The serotonergic antagonists at the above mentioned doses did not modify the food intake of animals not treated with methamphetamine, except for methiothepin, which produced a significant reduction, and mianserin, which produced a significant increase in food intake. The results of the present study indicated that the anorectic activity induced by methamphetamine is related to the interactions of methamphetamine with 5-HT receptor. Since a very small dose (0.003 micromolkg(-1)) of ondansetron (the 5-HT(3) antagonist), as compared with the other antagonists used in this study, antagonized the anorexia induced by methamphetamine, the 5-HT(3) receptor is likely to be the site for this interaction.

PMID: 15661576 [PubMed - indexed for MEDLINE]

3: J Physiol Pharmacol. 2004 Jun;55(2):357-69.

Involvement of some 5-HT receptors in methamphetamine-induced locomotor activity in mice.

Ginawi OT, **Al-Majed AA**, **Al-Suwailem AK**, **El-Hadiyah TM**.

Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. otginawi@hotmail.com

Effects of some selective 5-HT antagonists on methamphetamine-induced locomotor activity were investigated in male mice in order to study whether this effect of methamphetamine is selectively or at least partially, induced through stimulation of a specific serotonin receptor subtype. Methamphetamine (1.5 mg/kg, IP) produced a significant increase in locomotor activity. Methamphetamine-induced hyperactivity by the above mentioned dose was significantly antagonized by NAN-190 (5-HT(1A) antagonist) at a dose of 4 mg/kg, IP, methiothepin (5-HT(1B/1D) antagonist) at a dose of 0.1mg/kg, IP or mianserin (5-HT(2C) antagonist) at a dose of 8 mg/kg, IP. On the other hand, methysergide (5-HT(2A/2B) antagonist) at a dose of 1mg/kg, IP or ondansetron (5-HT(3) antagonist) at a dose of 0.5mg/kg, IP potentiated the methamphetamine-induced hyperactivity. None of the above mentioned doses of 5-HT antagonists altered the spontaneous activity of mice when administered alone. The results of the present study indicate a possible role for serotonergic mechanisms, in addition to the catecholaminergic systems, in the locomotor stimulant activity of methamphetamine in mice. This role is possibly mediated through direct stimulation of some 5-HT receptor subtypes. Stimulation by methamphetamine of 5-HT(1A), 5-HT(1B/1D) and/or 5-HT(2C) receptor subtypes may result in hyperactivity, whereas stimulation by methamphetamine of 5-HT(2A/2B) and/or 5-HT(3) receptor subtypes may result in decreased activity.

PMID: 15213358 [PubMed - indexed for MEDLINE]

4: Pharmacol Res. 2003 Sep;48(3):237-40.

Possible involvement of opioid receptors in moclobemide-induced hypothermia in mice.

Ginawi OT.

Department of Pharmacology, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia. otginawi@hotmail.com

Effect of moclobemide, a selective monoamine oxidase-type A enzyme inhibitor, was investigated on the body temperature of male mice. Moclobemide (15-30 mg kg(-1), i.p.) produced significant reductions of body temperature in both normal and yeast-induced hyperthermic male mice. The hypothermic effect of moclobemide was moderate and short-lasting. Moclobemide-induced hypothermia was not antagonized by previous administration of prazosin (10 and 20 mg kg(-1), s.c.), propranolol (5, 10, and 20 mg kg(-1), s.c.), haloperidol (2 and 10 mg kg(-1), s.c.), atropine (10 and 20 mg kg(-1), s.c.), mepyramine (25 and 50 mg kg(-1), s.c.), or methysergide (0.5, 1, and 2 mg kg(-1), s.c.). Pretreatment with the opioid antagonist naloxone (10 mg kg(-1), s.c.), however, was able to reverse the hypothermic effect of moclobemide (30 mg kg(-1), i.p.) in both normal and yeast-induced hyperthermic mice. The present results indicate a possible role for central opioid receptors in the hypothermic effect of moclobemide. Also, a peripheral component for this effect of moclobemide at the mitochondria of peripheral tissues is suspected. The peripheral tissue mitochondria could be considered a common target for moclobemide and opioids actions on body temperature.

PMID: 12860440 [PubMed - indexed for MEDLINE]

5: Res Commun Mol Pathol Pharmacol. 2001;110(3-4):239-51.

Effects of volatile oil constituents of Nigella sativa on carbon tetrachloride-induced hepatotoxicity in mice: evidence for antioxidant effects of thymoquinone.

Mansour MA, **Ginawi OT**, **El-Hadiyah T**, **El-Khatib AS**, **Al-Shabanah OA**, **Al-Sawaf HA**.

Department of Pharmacology, College of Pharmacy, King Saud University, PO Box 2457, Riyadh 11451, Saudi Arabia.

Effects of the volatile oil constituents of Nigella sativa, namely, thymoquinone (TQ), p-cymene and alpha-pinene, on carbon tetrachloride (CCl4-indued acute liver injury were investigated in mice. A single dose of CCl4 (15 microl/Kg i.p.) induced hepatotoxicity 24 h after administration manifested biochemically as significant elevation of the enzymes activities of serum alanine transaminase (ALT, EC:2.6.1.2), asparate transaminase (AST, EC:2.6.1.1) and lactate dehydrogenase (LDH, EC: 1.1.1.27). The toxicity was further evidenced by a significant decrease of non-protein sulfhydryl(-SH) concentration, and a significant increase of lipid peroxidation measued as malondialdhyde (MDA) in the liver tissues. Administration of different doses of the TQ (4, 8, 12.5, 25 and 50 mg/Kg i.p.) did not alter the chosen biochemical parameters measured, while higher doses of TQ were lethal. The LD50 was 90.3 mg/Kg (77.9-104.7, 95% CL). Pretreatment of mice with different doses of TQ 1 h before CCl4 injection showed that the only dose of TQ that ameliorated hepatotoxicity of CCl4 was 12.5 mg/Kg i.p. as evidenced by the significant reduction of the elevated levels of serum enzymes as well as hepatic MDA content and significant increase of the hepatic nonprotein sulfhydryl(-SH) concentration. Treatment of mice with the other volatile oil constituents, p-cymene or alpha-pinene did not induce any changes in the serum ALT measured. In addition, i.p. administration of these compounds 1 h before CCl4 injection, did not protect mice against CC4-induced hepatotoxicity. The results of the present study indicate that TQ (12.5 mg/Kg, i.p.) may play an important role as antioxidant and may efficiently act as a protective agent against chemically-induced hepatic damage. In contrast, higher doses of TQ were found to induce oxidative stress leading to hepatic injury.

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6: Gen Pharmacol. 1997 May;28(5):727-31.

Increased toxicity of methamphetamine in morphine-dependent mice.

Ginawi OT, al-Shabanah OA, Bakheet SA.

Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia.

1. The effect of methamphetamine on morphine-dependent mice was investigated by calculating the LD50 (i.p.), measuring motor activity, anorectic actions, and body temperature. 2. Methamphetamine was more toxic in morphine-dependent mice (LD50 = 20.6 mg/kg) than in normal mice (LD50 = 43.2 mg/kg). 3. Methamphetamine-induced locomotor activity was greater in morphinized than in nonmorphinized mice at doses of 2.5 and 5 mg/kg i.p. 4. Methamphetamine also increased the body temperature of morphinized mice more than that of normal mice ($P < 0.05$). 5. These findings suggest that methamphetamine is more toxic in morphine-dependent than in nondependent mice.

PMID: 9184810 [PubMed - indexed for MEDLINE]

7: Pharmacol Res. 1995 May;31(5):299-303.

Effect of (-)-cathinone, a psychoactive alkaloid from khat (Catha edulis Forsk.) and caffeine on sexual behaviour in rats.

Taha SA, **Ageel AM**, **Islam MW**, **Ginawi OT**.

Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

The effect of (-)-cathinone, caffeine and their combinations was studied on the sexual behaviour of male rats. Male sexual activities were assessed by recording the erectile responses (grooming of genitalis, yawning/stretching and homosexual mounting), in the absence of females. The copulatory behaviour was observed by caging males with receptive females brought into oestrus with s.c. injection of oestradiol benzoate and progesterone. The copulatory pattern of male rats (mounting, intromissions, ejaculations and refractory period) was recorded. The oral treatment of cathinone (5 mg kg-1 day-1), caffeine (50 mg kg-1 day-1) and their combinations for 15 days increased arousal (motivation) in male rats as evidenced by increased mounting performance and anogenital investigatory behaviour. However, erectile and ejaculatory responses, measured in the present study, showed no stimulant effect. It is conceivable from the present results that cathinone, the psychostimulant constituent of khat modified masculine pattern behaviour and caffeine also changed the effect of cathinone when administered concomitantly. However, our data provide no evidence that cathinone could be considered as an aphrodisiac.

PMID: 7479527 [PubMed - indexed for MEDLINE]

8: Neuropharmacology. 1993 Dec;32(12):1427-32.

The quipazine- and TFMPP-increased conditioned avoidance response in rats: role of 5HT1C/5-HT2 receptors.

Alhaider AA, **Ageel AM**, **Ginawi OT**.

Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

The role of serotonin (5-HT) in the acquisition of the conditioned avoidance response was investigated. The effects of different serotonin agonists and antagonists, administered prior to learning sessions, were studied in groups of naive rats using the two-way shuttle box. Quipazine, an agonist at 5-HT1B/1C/2 receptors, significantly increased avoidance responding in a dose-dependent manner (1.25-10 mg/kg, s.c.). The putative 5-HT1B/1C receptor agonist TFMPP (1-[m-trifluoromethylphenyl] piperazine) at doses of 1.25 and 2.5 mg/kg (s.c.), increased acquisition of conditioned avoidance but showed no significant difference from control at doses of 5 and 10 mg/kg. The 5-HT1A agonist, buspirone, significantly decreased acquisition of conditioned avoidance. Increased acquisition of conditioned avoidance induced by either quipazine or TFMPP was effectively antagonized by the mixed 5-HT 1C/2 receptor antagonists, ketanserin (0.2 and 2 mg/kg, s.c.) and mianserin (1 mg/kg, s.c.). In contrast, spiperone (5-HT1A/2 receptors antagonist: 0.2 mg/kg, s.c.) only inhibited the increased acquisition induced by TFMPP. On the other hand, the 5-HT1A/1B receptors antagonist, pindolol, failed to antagonize the increase in acquisition of conditioned avoidance caused by quipazine or TFMPP. These results suggest that quipazine increases the conditioned avoidance behaviour by an action that might be mediated through stimulation of 5-HT1C receptors. The acquisition of conditioned avoidance induced by TFMPP, which was blocked by ketanserin, mianserin and spiperone but not by pindolol, suggests the involvement of 5-HT1C/2 receptors in the action of TFMPP.

PMID: 8152532 [PubMed - indexed for MEDLINE]

9: Arch Int Pharmacodyn Ther. 1992 Jul-Aug;318:13-20.

Morphine analgesia in normal and alloxanized mice.

Ginawi OT.

Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

The analgesic response to 10 mg/kg of morphine hydrochloride, administered intraperitoneally, was examined in mice made diabetic by treatment with alloxan using the hot plate method. The hot plate base line latency of diabetic mice was significantly higher than that of normal mice. Morphine was found to possess an hyperglycaemic effect in both normal and diabetic mice. A decreased analgesic response to morphine was observed in diabetic mice. The decreased response seemed to be associated with plasma glucose levels, since multiple injections of insulin replacement abolished the decrease in morphine analgesia in diabetic mice. However, a single injection of insulin or glucose loading did not modify morphine analgesia. Naloxone was an effective antagonist of the analgesic and hyperglycaemic effects of morphine in both normal and diabetic mice, but induced a greater reduction of the plasma glucose level in diabetic than in normal mice. It is suggested that a supranormal dose of morphine may be needed in diabetics.

PMID: 1361122 [PubMed - indexed for MEDLINE]

10: Arzneimittelforschung. 1990 Nov;40(11):1242-5.

Synthesis and antinociceptive activity of ring substituted N-[(2-phenyl-2-hydroxy)ethyl]-4-phenyl-4-carboethoxypiperidines.

al-Rashood KA, **Madani AE**, **Ginawi OT**, **Ashraf SA**, **el-Obeid HA**.

Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

A series of phenyl substituted N-[(2-phenyl-2-hydroxy)ethyl]-4-phenyl-4-carboethoxylpiperidine were synthesized and their antinociceptive activity tested in mice and compared with morphine sulphate. All compounds demonstrated antinociceptive activity in both the hot plate and the writhing tests. The studies showed that the antinociceptive activity is dependable on both the nature and the position of the substituent on the phenyl ring. Antagonism study with naloxone suggests possible interaction of the new compounds with the opioid receptors.

PMID: 2085338 [PubMed - indexed for MEDLINE]

11: J Pharm Sci. 1988 Oct;77(10):898-901.

Antipsychotic properties of new N-(4-substituted-1-piperazinylethyl)- and N-(4-substituted-1-piperidinylethyl)-phthalimides.

al-Rashood KA, **Mustafa AA**, **Alhaider AA**, **Ginawi OT**, **Madani AA**, **el-Obeid HA**.

College of Pharmacy, Department of Pharmaceutical Chemistry, King Saud University, Riyadh, Saudi Arabia.

A series of N-(4-phenyl- and 4-pyridyl-1-piperazinylethyl)- and N-(4-phenyl-1-piperidinylethyl)-phthalmides were synthesized and tested for antipsychotic activity. All compounds suppressed the spontaneous motor activity and the apomorphine-induced climbing in mice and pergolide-induced locomotor activity in rats, demonstrating psychotropic properties equal to the corresponding properties of sulpiride. Although the compounds, like sulpiride, were less potent than haloperidol in blocking the locomotor activities, they caused no catalepsy, a major side effect following treatment with conventional antipsychotic agents. It is likely that the new compounds produce their neuroleptic activities through inhibition of limbic dopamine receptors.

PMID: 2907047 [PubMed - indexed for MEDLINE]

12: Res Commun Chem Pathol Pharmacol. 1986 Nov;54(2):201-9.

Some central effects of indenolol in experimental animals.

Tariq M, **Babhair SA**, **Ageel AM**, **Ginawi OT**, **Parmar NS**.

Indenolol, a relatively new beta-adrenergic blocking drug, was tested for its effect on the central nervous system. The parameters included its effects on spontaneous motor activity, conditioned avoidance response (CAR) acquisition, pentobarbitone hypnosis, amphetamine induced motor excitation, analgesic activity and rectal temperature in experimental animals. Indenolol was found to significantly decrease the spontaneous motor activity in mice and CAR acquisition in rats. It potentiated the pentobarbitone induced hypnosis and antagonized amphetamine induced excitatory behaviour in mice. It did not show a marked analgesic effect of its own but potentiated the analgesia induced by the subanalgesic dose of morphine. It also produced a significant hypothermic effect in mice. All the effects except on CAR acquisition were obtained in the dose of 50-75 mg/kg body weight administered intraperitoneally. It enhanced CAR acquisition in the specific dose of 5 mg/kg. These observations indicate that indenolol possesses an anxiolytic effect similar to that reported for propranolol and some other beta-blocking drugs.

PMID: 2878478 [PubMed - indexed for MEDLINE]

13: Jpn J Pharmacol. 1985 Feb;37(2):137-42.

Effects of methamphetamine and methyldopa on ethanol induced hypothermia in mice.

Ageel AM, **Ginawi OT**.

The effects of D-methamphetamine HCl (1, 2 and 4 mg/kg, i.p.) and alpha-methyldopa (1, 2 and 4 mg/kg, i.p.) on rectal temperature and on ethanol (3 g/kg, i.p.)-induced hypothermia have been investigated in mice. Methamphetamine caused a dose-dependent hyperthermia, but methyldopa induced hypothermia, which decreased with increases in dose. Methamphetamine antagonized the hypothermic effect of ethanol, but methyldopa (1 and 2 mg/kg) did not affect it. Methyldopa (4 mg/kg), however, reversed ethanol hypothermia. Ethanol pretreatment significantly potentiated the hypothermic effect of methyldopa (4 mg/kg), and it prevented methamphetamine-induced hyperthermia. A possible central action for the tested drugs on biogenic monoamines and a peripheral component in their thermoregulatory effects are discussed in this report.

PMID: 3999469 [PubMed - indexed for MEDLINE]