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RESEARCH ARTICLE

New Derivatives from Phencyclidine Increase Food and Water Intake in Wistar Rats

A. AHMADI, J. SOLATI and M. KHALILI

For author affiliations, see end of text.

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ABSTRACT

Phencyclidine (1-(1-phenylcyclohexyl) piperidine, CAS 956-90-1, PCP, I) and its derivatives have shown many pharmacological and behavioral effects. Also, food and water intake of many drugs such as PCP and its analogues have been studied in laboratory animals. In this work, two derivatives (II, III) of phencyclidine were tested for feeding behaviors effects on rats and compared to PCP and vehicle (saline). The results showed that, both derivatives can increase food and water intake in comparison to the PCP and vehicle (control) groups that have measured 1-12 h for food and 30–180 min for water intake after injection.

Keywords: *Phencyclidine derivatives, Pharmacological effects, Food and water intake*

Phencyclidine (1-(1-phenylcyclohexyl) piperidine, CAS 956-90-1, PCP, I) (Scheme 1) and its derivatives display analgesic [1-8], stimulant [9,10], anticonvulsant [11,12] and behavioral effects [13-15] because of specific binding sites in the brain [14]. PCP binds to the N-methyl-D-asparate (NMDA) receptor complex and blocks NMDA-mediated gating of the calcium channel conductance [15,16]. These have many common behavioral effects with other phencyclidine-like drugs, including anaesthetics, antinociceptives, psychotomimetics, anticonvulsants, neuroprotectives and amnesic drugs due to non-competitive "open channel blocking" of the NMDA receptor [17].

Food and water intake as a model of behavioral effects of many drugs such as PCP and its analogues, morphine, amphetamine, dexfenfluramine and diazepam, have been studied in laboratory animals [18-35]. Various brain systems are involved in behavioral effects of them [15,16]. Previous studies showed the important role of nicotine and nicotinic acetylcholine receptors on feeding behaviors of animals. PCP analogues have been shown the inhibition of nicotinic acetylcholine receptor channels (nAChR) in rats [36-42]. The recent studies also showed that NMDA receptor antagonists like PCP have direct effects on serotonin (5-HT) receptors and that systemic PCP treatment elevates brain extracellular 5-HT level by interaction with 5-HT reuptake site [16,18]. Serotonin has been extensively implicated in an array of behavioral and physiological functions including the control of ingestive behaviors [43,44].

Therefore; it seems that all of the NMDA glutamatergic system, nicotinic acetylcholine receptors and serotonin (5-HT) receptors have very important role on modulation of feeding behavior [16,18,36-43]. In this work, two methyl and methoxy hydroxyl derivatives of Phencyclidine [45] [(1-[1-(4-methylphenyl) (cyclohexyl)] 4-piperidinol, II), (1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol, III)] were tested for food and water intake in rats and were compared with PCP and vehicle.

MATERIALS AND METHODS

Cyclohexanone, Piperidine, Bromobenzene, magnesium turning, diethyl ether, 4-bromo toluene, 4-bromo anisole, 4-piperidinol and all other chemicals were purchased from Merck Chemical Co (Darmstadt, Germany). Melting points (uncorrected) were determined using a digital Electrothermal melting point apparatus **(**model 9100**,** Electrothermal Engineering Ltd**.,** Essex, UK**).** ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded on a Thermo Nicolet FT-IR (model Nexus-870, Nicolet Instrument Corp, Madison, Wisconsin, USA) spectrometer. Mass spectra were recorded on an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmigton,

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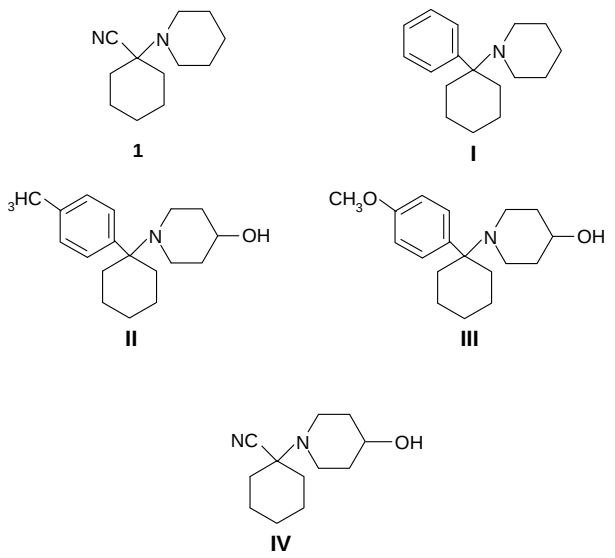

Scheme 1. Structure formulas of PCP (**I**), PCP-CH_3-OH (**II**), PCP-OCH_3-OH (**III**) and Carbonitrile intermediates **1** and **IV**.

USA). Column chromatographic separations were performed over Acros silica gel (No. 7631-86-9 particle size 35-70 micrometer, Geel, Belgium). Adult male Wistar rats (Pasteur's Institute, Tehran, Iran), weighing 220 -260 g were used for pharmacological testing.

Preparations (Scheme 1)

4-hydroxypiperidinocyclohexylcarbonitrile IV: This compound was prepared in an organic solvent from 4-piperidinol, cyclohexanone and KCN [46].

(1-(1-phenylcyclohexyl) piperidine (PCP) I: This compound was prepared from 1-piperidinocyclohexanecarbonitrile (1) and phenyl magnesium bromide. The hydrochloride salt of I was prepared using 2-propanol and HCl and was re-crystallized from 2-propanol [47].

1-(4-methylphenyl) (cyclohexyl) 4-piperidinol II: This compound was prepared from nitrile compound (IV) and *p*-tolyl magnesium bromide (Grignard reagent) according to a published method [45]. The hydrochloride salt of II was prepared using 2-propanol and HCl and was recrystallized from 2-propanol [45].

1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol III: This compound was prepared from nitrile compound (IV) and *p*-anisol magnesium bromide (Grignard reagent) according to a published method [45]. The hydrochloride salt of III was prepared using 2-propanol and HCl and was re-crystallized from 2-propanol [45].

Pharmacological methods

Adult male Wistar rats (Pasteur's Institute, Tehran), weighing 220 -270 g were housed in individual polypropylene cages under controlled temperature (25°C) and light (12 h: 7 am to 7 pm)/dark (12 h) cycle with ad libitum access to food (standard laboratory rat chow, Pars company, Tehran, Iran) and water. The experimental procedures adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH) and those of the Research Council of Biology Department of Karaj Islamic Azad University (Karaj, Iran).

Food intake study

In this experiment, the four groups of animals after 1 week of habituation to their new housing conditions were deprived of food for 24 h (rats were fasted in separate cages with free access to water), three groups were IP-injected with drugs (I, II, III) hydrochloride (5 mg/kg, that is under LD_{50} limit dosage of PCP and its analogues [5], solved in 0.2 ml saline) and another group received equivalent volume of saline. The number of rats was six in each group. Immediately after injection, each rat was returned to its cage and a weighed hopper of food was placed in the cage. The quantities of cumulative food (standard laboratory rat chow) consumed were measured 1-12 h after injection of the solutions.

Water intake study

Rats had free access to water and food and were put in the separate metabolic cages at least 7 days before the experiments. The amount of water ingested in the various experiments was measured with 0.1 ml graduated glass burettes adapted with a metal drinking spout. Intake was induced by water deprivation during the 24 h that preceded the experiment. Four groups of animals were deprived of water, three groups were IP-injected with drugs (I, II, III) hydrochloride (5 mg/kg, that is under LD_{50} limit dosage of PCP and its analogues [5], solved in 0.2 ml saline and another group received equivalent volume of saline. The number of rats was six in each group. Immediately after injection, each rat was returned to its cage and cumulative water intake was measured 30–180 min after injection of the solutions.

Intraperitoneal (IP) injection of saline and drugs

At the beginning of the experiment, the animals were injected (5 mg/kg, ip) with saline (vehicle), and PCP (I), PCP-CH_3-OH (***II***), PCP-OCH_3-OH (***III***) hydrochloride that were dissolved in saline.

Statistical analysis

The differences between vehicle, PCP and derivatives were evaluated using analysis of variance method (ANOVA). The p value < 0.05 was considered to represent significant difference. The cumulative food and water intake were measured (1-12 h for food and 30–180 min for water) after injection of the solutions.

RESULTS

Chemistry

Phencyclidine **(I),** 1-[1-(4-methylphenyl) (cyclohexyl) 4-piperidinol (II**)** and 1-[1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol (III**)** were synthesized by reaction of substituted Grignard reagents and carbonitrile compounds [45]. This compounds (II**,**

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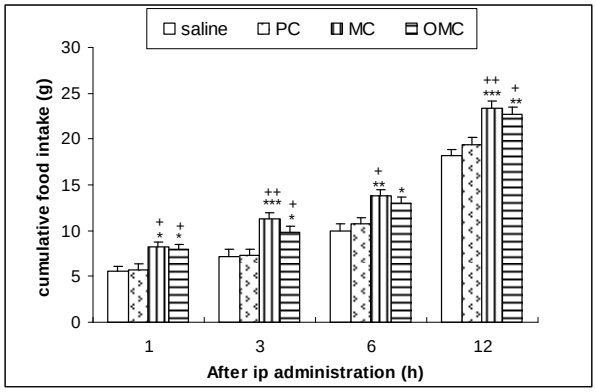

Fig 1. Effects of i.p. injection of PC (**I**), MC (**II**), and OMC (**III**) hydrochloride or saline (vehicle) (5 mg/kg) on cumulative food intake in food deprived rats (24 h), 1–12 h after injection of solutions. Data for food intake are expressed as the mean ± SEM (n = 6).*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ compared with saline-injected rats; $^{+}p < 0.05$ and $^{++}p < 0.01$ compared with PC.

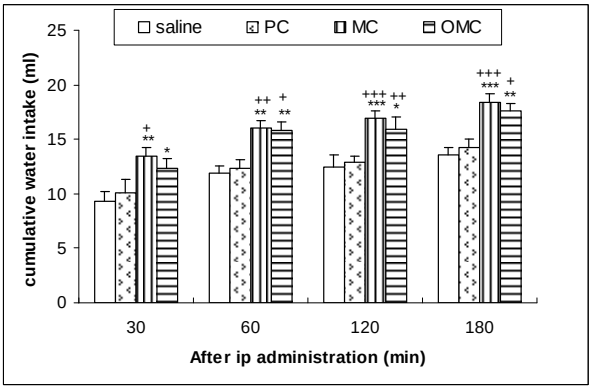

Fig 2. Effects of i.p. injection of PC (**I**), MC (**II**), and OMC (**III**) hydrochloride or saline (vehicle) (5 mg/kg) on cumulative water intake in water deprived rats (24 h), 30–180 min after injection of solutions. Data for water intake are expressed as the mean ± SEM (n = 6-9).*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ compared with saline-injected rats; $^{+}p < 0.05$, $^{++}p < 0.01$ and $^{+++}p < 0.001$ compared with PC.

III) have stronger hydrophilic and polarity (a hydroxyl group on the piperidine ring) and the high electron donating, distribution and dipole moments (a methyl (II) or methoxy (III) group on the aromatic ring) properties. Known procedures were applied for the synthesis of all compounds I-IV with the appropriate modifications described previously [46-48].

Pharmacology

General Consideration

Animal behavioral observation showed no mortality, morbidity, irritability and other side effects due to drugs administration. However, comparison of the motor coordination index (as measured by Rota-rod apparatus, Harvard, UK) indicated no significant differences between control and treatment rats.

The effect of PCP (I), 1-[1-(4-methylphenyl) (cyclohexyl) 4-piperidinol (II) and 1-[1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol (III) hydrochloride in food and water intake

The results showed that two derivatives of phencyclidine (II, III) can increase feeding consumption in comparison to the PCP and vehicle (control) groups in food- and water-deprived rats (24 h). In details, II increased food and water intake more than III with a marked significant increase in the intaking time (Figs 1-2). Also the most quantities were seen after 12 h for food and after 180 min. for water intake.

DISCUSSION

Results of present study showed that methyl and methoxy hydroxyl derivatives of Phencyclidine [45], [(1-[1-(4-methylphenyl) (cyclohexyl)] 4-piperidinol, II) and (1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol, III)], increase food and water intake in wistar rats. However, more studies are necessary for demonstration of mechanisms that under which this new derivatives can affect feeding behaviors.

As it mentioned before, PCP works primarily as an NMDA receptor antagonist, which blocks the activity of the NMDA receptor [15-17]. Some studies have shown that NMDA glutamatergic system has a role on modulation of feeding behaviors as systemic injection of the non-competitive NMDA antagonist, MK801, increased food intake in rats [49]. Cholinergic systems may also have a role in modulation behavioral effects of PCP derivatives and would be caused to increase food and water intake by inhibition of nicotinic acetylcholine receptor channels (nAChR). Other studies also demonstrated that nicotine administration and activation of nAChRs associated with decreased in food and water intake and lower body weight in rats [36-42].

PCP derivatives can also affect food and water intake by interaction with serotonergic system so that PCP administration increase brain serotonine level and affect different 5-HT receptors [16,18] and several studies have been shown the effects of serotonergic system and 5-HT receptors system in different brain regions on control of food and water intake [43, 44].

From above-mentioned studies, it can be concluded that various brain systems and receptors are involved in modulating behavioral effects of PCP and its analogues. As there was no report for PCP increasing food and water intake [13, 26], we applied two derivatives of this molecule with the changes in substitution on its phenyl and piperidine rings (II, III) that had more hydrophilic, polarity, electron distribution and dipole moments properties for increasing in feeding behavior [45, 48]. Therefore, it seems that strong electron donating properties of the methyl group on *para* position of phenyl ring and also hydrophilic and polarity properties of hydroxyl group on the piperidine ring of the molecule (II) facilitate increases affinity to receptors and it is anticipated that food and water intake could be increased in comparison with PCP and vehicle (control). Also, strong electron donating properties of the methoxy group on *para* position of phenyl ring and hydrophilic and polarity properties of hydroxyl group on the piperidine ring of the molecule (III) increased feeding

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consuming in comparison to the PCP and vehicle (control). Because of undesired reactions with cationoid intermediates [50], little decrease in receptor binding could be anticipated. This increase is less than that in II but still it is higher than PCP and vehicle (control).

Inconclusion, this study showed that both of two derivatives of phencyclidine (II, III) were more effective than PCP in modulation of feeding behavior in rats and appropriate substitution of the methyl, methoxy and hydroxyl groups may result in ligands with higher affinity for the PCP site on receptors.

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CURRENT AUTHOR ADDRESSES

A. Ahmadi, Department of Chemistry, Faculty of Science, Islamic Azad University, Karaj, Iran. E-mail: abbas_ahmady_3957@yahoo.com (Corresponding author)

J. Solati, 2Department of Physiology, Faculty of Science, Islamic Azad Universiy, Karaj, Iran.

M. Khalili, Department of Physiology, Faculty of Medicine, Shahed University, Tehran, Iran.

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