# A biphasic opioid function modulator: agmatine

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**KEY WORDS** agmatine; morphine; opioid receptors; imidazoline receptors; biphasic opioid function modulator; morphine dependence

## ABSTRACT

Recently it has been revealed that some agents that are not able to interact with opioid receptors play an important role in regulating the pharmacological actions of opioids. Especially, some of them show biphasic modulation on opioid functions, which enhance opioid analgesia, but inhibit tolerance to and substance dependence on opioids. We would like to call these agents which do not interact with opioid receptors, but do have biphasic modulation on opioid functions as biphasic opioid function modulator (BOFM). Mainly based on our results, agmatine is a typical BOFM. Agmatine itself was a weak analgesic which enhanced analgesic action of morphine and inhibited tolerance to and dependence on opioid. The main mechanisms of agmatine were related to inhibition of the adaptation of opioid receptor signal transduction induced by chronic treatment of opioid.

## INTRODUCTION

Opioids, such as morphine, are widely used in the clinical management of pain, which were not able to be substituted by other analgesics for near 200 years. Their clinical practice, however, is greatly limited, because of their powerful potential to induce tolerance and dependence. People have been fighting for a long time to find powerful analgesics like opioids without capacity of inducing tolerance and dependence by reforming opioid chemical structure or looking for other leading compounds from natural medicines, but so far nobody has got success in the research field.

Recently it has been revealed that some agents which are not able to interact with opioid receptors play an important role in regulating the pharmacological actions of opioids. Especially, some of them show biphasic modulation on opioid functions, which enhance opioid analgesia (positive action), but inhibit tolerance to and substance dependence on opioids (negative actions). The mechanisms associated with their biphasic modulation on opioid function as mentioned above might be related to their inhibitory actions on NMDA receptor system at different levels. These agents at least include imidazoline receptor agonist agmatine, *N*-methyl-*D*-aspartate (NMDA) receptor antagonists, NOS inhibitors, and voltage-dependent calcium channel blockers. We would like to call these agents which do not interact with opioid receptors, but do have biphasic modulation on opioid functions as biphasic opioid function modulator (BOFM)[1].

We think that suggestion of the new concept, BOFM, might have some importance in opioid basic and practical scientific research fields. It is going to set up a new field to research on the mechanisms of opioid tolerance and dependence, to set up a new field to research and develop new drugs for treatment of opioid tolerance and dependence, and to set up a new

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Received 2003-01-08 Accepted 2003-04-24

way to obtain powerful analgesia without or with lower potential to induce tolerance and dependence by a complex of BOFM with opioids[1].

Agmatine is an endogenous biological active substance, which is synthesized by decarboxylation of *L*-arginine catalyzed by *L*-arginine decarboxylase in mammals including human body. So far a widely received concept is that agmatine is a neurotransmitter and/or modulator, the biological and pharmacological actions of which are closely associated with imidazoline and NMDA receptors. It was first demonstrated by Kolesnikov and his colleagues that agmatine enhanced morphine analgesia and inhibited morphine tolerance in mice[2]. In nearly past 10 years, more and more accumulated results reported by our laboratory and others point out that agmatine has obvious actions on opioid functions, which is a very good example for BOFM.

In the short review, we would like to summarize the characteristics of agmatine as a BOFM, mainly based on our laboratory research works in this field in past 10 years.

## MODULATION OF EXOGENOUS AGMATINE ON THE OPIOID FUNCTIONS

**Analgesia** Agmatine had no analgesia in severe nociceptive experimental models, such as hot radiation tail flick test, under the dosage range from 0.1 to 62.5 mg/kg administered subcutaneously. It, however, showed obvious analgesic actions in a dose-dependent manner in some weak nociceptive experimental models such as acetic acid writhing test in mice or 4 % saline writhing test in rat. The $ED_{50}$ obtained in the two experiments were 10.1 (6.8-15.4) and 14.1 (8.4-23.8) mg/kg, respectively. These results indicated that agmatine had weak analgesic effects[3].

**Enhancement of opioid analgesia** Agmatine enhanced analgesia of morphine and clonidine in a dose-dependent manner. In the mouse and rat tail flick tests, with increase in the doses of agmatine (0.1-12.5 mg/kg), the possible maximal analgesic percentage (PMAP) of morphine 5 mg/kg was increased from 37 % to 92 % in mice and from 39 % to 71 % in rats. In mice tail flick test, agmatine elevated PMAP of morphine 2.5 mg/kg from 17 % to 60 %. In quantitative assay, agmatine decreased analgesic $ED_{50}$ of morphine or clonidine by over 75 % as compared with normal saline group. Co-administration of agmatine (12.5 μg for each animal) with different dosages of morphine by intracerebroven-tricular (icv) or intrathecal (it) injection potentiated analgesic effect of morphine, but the potencies of the effects between icv and it injection of agmatine were quite different in mouse tail flick test. Intrathecal injection of agmatine decreased analgesic $ED_{50}$ of morphine by over 94 % (from 681 to 46 ng per animal), while icv injection of agmatine only decreased $ED_{50}$ of morphine analgesia by 75 % (from 201 to 51 ng per animal). Although agmatine 10 mg/kg enhanced morphine analgesia, it did not prolong the analgesic time in mouse tail flick test. At 240 min after administration (sc) of normal saline plus morphine or agmatine plus morphine, PMAPs were less than 20 %[3].

**Inhibition of opioid tolerance** Electrical field stimulation induced twitch contractions of ileum longitudinal smooth muscle (GPILSM) of guinea pig *in vitro*. Morphine concentration-dependently inhibited the contractions, the $IC_{50}$ was 156 (95 % CL: 125-169) nmol/L. Pretreatment of GPILSM with morphine 270 nmol/L for 8 h induced a tolerance indicated by a 38-fold increase in the $IC_{50}$ value (from 156 to 5864 nmol/L) of morphine. Co-incubation of the preparation with agmatine and morphine prevented the development of tolerance to morphine indicated by restore of GPILSM sensitivity to the inhibitory effect of morphine. These results first showed the evidences to prove that agmatine inhibited tolerance to opioid *in vitro*[4].

In qualitative tolerance experiments, agmatine prevented the development of opioid tolerance *in vivo*. When mice were chronically pretreated with morphine or hydroxycodone for 7 to 9 d, their responses to the analgesia of morphine or hydroxycodone were decreased at the lowest point by d 5, respectively. Co-administration of agmatine at 0.13, 1.25, and 2.5 mg/kg with morphine or with hydroxycodone prevented the decrease in analgesic actions of morphine or hydroxycodone compared with those pretreated with morphine or hydroxycodone alone, respectively[5]. In quantitative tolerance experiment, either repeated or single large dose administration of morphine (100 mg/kg, sc) induced an increase in its analgesic $ED_{50}$ by about 3-fold compared with that in naive mice. Co-administration of agmatine with morphine was able to prevent the increase in a dose-dependent manner. The analgesic $ED_{50}$ of morphine obtained from the mice pretreated with the highest dose of agmatine (2.5 mg/kg) plus morphine had no significant difference compared with that of naive mice[5].

The tolerance induced by single large dose of

morphine (100 mg/kg) in mouse tail flick test persisted at least over 72 h. At 6, 24, 48, and 72 h after administration of single large dose of morphine (100 mg/kg), agmatine (10 mg/kg) was given by sc. A single dose of agmatine (6 h group) attenuated the tolerance and restored the sensitivity of mice to morphine analgesia. With increase in the time after administration of agmatine, PMAPs recovered gradually to the level in naive mice. These results indicated that agmatine had not only preventive but also therapeutic actions on opioid tolerance induced by chronic or acute pretreatment with opioids in mice and rats[5].

Administration of agmatine by icv or it inhibited the tolerance induced by a single large dose of morphine in mice, but the potencies of inhibition of the acute tolerance by agmatine were quite different. The inhibitory effects of agmatine administered by icv was much more powerful than that administered by it, indicating that the main site of agmatine for inhibition of opioid tolerance was at upper central nervous system[6].

**Inhibition of opioid substance dependence** Pretreatment of GPILSM with morphine (270 nmol/L) for 8 h induced substance dependence indicated by a precipitated contractive response to naloxone *in vitro*. Co-incubation of the preparation with agmatine and morphine inhibited the development of the substance dependence indicated by a complete inhibition of the precipitated contractive response to naloxone. These results first proved that agmatine inhibited substance dependence on morphine *in vitro*[4].

After pretreatment of the mice with morphine or hydroxycodone for 3-7 d in different pretreatment models, naloxone was able to precipitate a very clear-cut abstinent syndrome indicated by an increase in jump percentage and jump number and loss in body weight. Co-administration of morphine or hydroxycodone with agmatine inhibited the abstinent syndrome induced by naloxone significantly. At the dosage of 10 mg/kg by sc or 40 mg/kg by *po*, agmatine could evoke a decrease in jump percentage by 80 %-100 %, jump number by 70 %-100 % compared with morphine alone, respectively. In addition, agmatine showed a very similar inhibitory effect on abstinent syndrome precipitated by naloxone in morphine-dependent rats[5].

The dosage of naloxone required to precipitate abstinent syndrome was in inverse ratio to the severity of abstinent syndrome. $ED_{50}$ of naloxone to induce abstinent syndrome in morphine-dependent mice was about 2.5 mg/kg. Pretreatment of morphine-dependent mice with agmatine induced an increase in $ED_{50}$, the dose of naloxone to precipitate half morphine-dependent animals in abstinent syndrome, in a dose-dependent manner. Co-administration of agmatine 10 mg/kg (tid, for 3 d) with morphine prevented the development of substance dependence and increased $ED_{50}$ of naloxone required for inducing withdrawal syndrome[5].

## POSSIBLE MECHANISMS OF EXOGENOUS AGMATINE ON THE OPIOID FUNCTIONS

From the above studies, we know that agmatine enhanced morphine analgesia, it had both preventive and therapeutic effects on the development of tolerance to and substance dependence on morphine. The essence of tolerance to and substance dependence on opioids is adaptation, which might occur in prereceptor (alteration of neurotransmitters), receptor (change of the quantity and quality of receptor), and postreceptor (change of the signal transduction systems). Based on this hypothesis, we studied the possible mechanisms at these three levels.

**Inhibition of release of monoamine neurotransmitters from different brain areas** When the slides of different brain areas of morphine-dependent rats were precipitated by naloxone *in vivo*, the release of monoamine neurotransmitters including noradrenaline, dopamine acid, dopamine, and 5-HIAA in striatal and thalamus, noradrenaline, dopamine acid, and 5-HIAA in the hippocampal slices, was increased significantly. Co-administration of agmatine 5-20 mg/kg with morphine inhibited the abstinent score of morphine-dependent rats precipitated by naloxone. Simultaneously, the co-administration also inhibited the increase in release of monoamine neurotransmitters induced by naloxone. The inhibition of abstinent syndrome by agmatine was parallel to the inhibitory effects of agmatine on release of the monoamine neurotransmitters. The inhibitory effects of agmatine could be antagonized by idazoxan, suggesting the participation of imidazoline receptor[7].

**No action on [$^3$H]naloxone binding with opioid receptors** Chronic treatment of rats with morphine induced a down-regulation of opioid receptors and a decrease in binding affinity to [$^3$H]naloxone. The $K_d$ value increased 4-fold, and the $B_{max}$ decreased by 30.6 %. Although agmatine inhibited the abstinent syndrome of morphine-dependent rats as mentioned above, it did not significantly influence the $K_d$ and $B_{max}$ values

of opioid receptors. On the other hand, morphine inhibited the binding of opioid receptors to [$^3$H]naloxone in a dose-dependent manner, agmatine, however, did not inhibit the binding of opioid receptors to [$^3$H]naloxone any more. These results indicated that agmatine did not directly or indirectly interact with opioid receptors[8].

**Inhibition of NOS activity**

Substrate competitive inhibition NOS activity was determined in cerebellum, forebrain, and thalamus for naive mice, which were (230±22), (46±29), and (135±53) pmol [$^3$H]citrulline· min$^{-1}$· g$^{-1}$ (protein), respectively. After direct administration of agmatine to the measurement system of NOS activity, the activities of NOS in cerebellum, forebrain, and the thalamus of naive mice were inhibited in a concentration-dependent manner, agmatine 100 μmol/L inhibited the NOS activity in cerebellum, forebrain, and thalamus by 66.4 %, 73.7 %, and 70.4 %, respectively. In the Lineweaver-Burk plot, the $K_m$ of NOS increased as increase in the antagonist concentration while the $V_{max}$ was not changed. In the Dixon plot, with the increase of the substrate concentration, the velocity of the enzyme reaction increased. The effects were not antagonized by idazoxan. These results revealed that the inhibitory effect of agmatine on NOS was substrate competitive[9].

Inhibitory effect of NOS activity by activation of imidazoline receptor After the mice were pretreated with morphine for 5 d, naloxone induced significant abstinent syndrome. At the same time, the NOS activity was significantly increased in the cerebellum, forebrain, and thalamus by 2-3 times compared with control. Co-pretreatment of mice with morphine plus agmatine inhibited the increase in NOS activity in cerebellum, forebrain, and thalamus induced by naloxone. Agmatine 10 mg/kg inhibited the NOS activity in cerebellum, forebrain, and thalamus by 55.4 %, 52.0 %, and 66.0 % compared with morphine-treated group, respectively. The inhibitory effect of agmatine was antagonized by idazoxan. This result indicated that agmatine could inhibit NOS activity by the activation of imidazoline receptor (I-R)[9].

Influence of agmatine on the GTPγS binding stimulated by opioids Agmatine inhibited the rapid desensitization caused by opioids. Pretreatment of NG108-15 cell with morphine 100 μmol/L for 10 min induced a rapid desensitization, indicating a decrease in stimulation action of morphine 10 μmol/L on [$^{35}$S]GTPγS binding. When the cells were pretreated with 1 or 10 μmol/L agmatine and morphine, the desensitization induced by preincubation with morphine was inhibited in a concentration-dependent manner. Idazoxan dose-dependently antagonized the inhibitory effect of agmatine 10 μmol/L on morphine-induced rapid desensitization[10].

Agmatine also inhibited chronic tolerance to morphine. Pretreatment of NG108-15 cell with morphine 100 μmol/L for 8 h, the [$^{35}$S]GTPγS binding stimulated by morphine was decreased, the dose-response curves were shifted to right, and the maximum actions were decreased. Co-pretreatment of NG108-15 cell with morphine plus agmatine 10 μmol/L inhibited the development of tolerance to morphine, the stimulating effect of morphine on [$^{35}$S]GTPγS binding was increased significantly compared with morphine-treated cells, the difference of maximum stimulating effect was not significant compared with normal saline group. Idazoxan 100 nmol/L inhibited the effect of agmatine significantly. The dose-response curves were shifted to right compared with the agmatine plus morphine pretreatment group, suggesting the participation of I-R[10].

**Influence of agmatine on cAMP concentration** Agmatine enhanced the inhibitory effects of morphine on cAMP concentration in NG108-15 cells. Agmatine itself inhibited the increase of cAMP concentration under the stimulation of Forskolin only at the concentration of 1 mmol/L. At the concentration of 1-100 μmol/L, agmatine enhanced the inhibitory effects of morphine on the increase of cAMP concentration stimulated by Forskolin. In the presence of agmatine 10 μmol/L, the inhibitory potency of morphine on cAMP concentration stimulated by Forskolin was increased by 100 %[10].

Agmatine inhibited rapid desensitization of NG108-15 induced by pretreatment of morphine. Pretreatment of NG108-15 cells with morphine 100 μmol/L evoked rapid desensitization, characterized by decreasing inhibitory effects of morphine on cellular cAMP concentration stimulated by Forskolin. When the cells were pretreated with different concentrations of agmatine plus morphine, the inhibitory effect of morphine on Forskolin-stimulated increase in cAMP concentration in NG108-15 cell restored as the cells treated with normal saline. Co-pretreatment of NG108-15 cells with idazoxan 100 nmol/L plus agmatine plus morphine antagonized the effect of agmatine, the cAMP concentration was increased significantly compared with that preincubated with agmatine plus morphine group[10].

Agmatine inhibited the cAMP overshooting of morphine-dependent cells precipitated by naloxone. Pretreatment of NG108-15 cells with morphine 100 μmol/L for 24 h evoked a 2.5-fold increase in cellular cAMP concentration precipitated by naloxone compared with control. When the cells were pretreated with agmatine 10 μmol/L plus morphine for 24 h, morphine completely lost the ability to induce the cellular cAMP overshooting. The inhibitory effect of agmatine on cAMP over-shooting was antagonized by idazoxan in a concentration-dependent manner[10].

**Inhibition of electrical dependent calcium channel** Agmatine was able to inhibit electrical dependent calcium channel in hippocampus neurons in a concentration-dependent manner. At 50 μmol/L, agmatine blocked calcium current completely. The inhibitory effect of agmatine on calcium current was partially antagonized by idazoxan[11].

## EFFECT OF ENDOGENOUS AGMATINE ON OPIOID FUNCTION

Since exogenous agmatine modulated opioid functions and agmatine is the endogenous ligand of imidazoline receptors, it is possible that endogenous agmatine might have the same effects to modulate opioid functions. Based on this hypothesis, when we managed to change the quantity of endogenous agmatine, the pain threshold and functions of opioid might also be influenced.

**Influence of idazoxan on the pharmacological effects of morphine** Idazoxan is a selective antagonist of imidazoline receptors and it might inhibit the effects of endogenous agmatine through blockage of imidazoline receptor. In our study we found that idazoxan lowered the pain threshold in a dose-dependent manner. Idazoxan 9 mg/kg lowered the pain threshold by about 120 % and 61 % in mouse acetic acid writhing test and mouse 55 °C hot plate test, respectively. In addition, idazoxan dose-dependently inhibited morphine analgesia. Idazoxan 9 mg /kg decreased PMAP for about 88.9 % and 38 % in mouse acetic acid writhing test and mouse 55 °C hot plate test, respectively. Moreover, idazoxan promoted the development of morphine tolerance. In mouse heat radiation tail flick assay and mouse 55 °C hot plate test, the PMAP of morphine was decreased significantly after chronic treatment of the animals with large dose of morphine, co-administration of idazoxan 9 mg/kg further reduced the PMAP of morphine 5 mg/kg. The PMAP of morphine 5 mg/kg was decreased by 26 % and 34 % in these two models compared with morphine pretreatment group, respectively. As naloxone, idazoxan induced abstinent syndrome in morphine-dependent mice and rats. Compared with the saline group, idazoxan 9 mg/kg increased the jumping number of morphine-dependent mice for 9-fold and increased the abstinent score of morphine-dependent rats by 13-fold[12].

**Effect of *L*-arginine on morphine functions** *L*-arginine is the substrate of endogenous agmatine, so it is possible that the concentration of endogenous agmatine might increase after administration of *L*-arginine and exerted the same effects on opioid function like exogenous agmatine. We found that *L*-arginine (0.5-50 mg/kg, sc) exhibited no analgesia and did not influence analgesia of and tolerance to morphine. The reason may be related to the different metabolism routes of *L*-arginine[13].

**Influence of *L*-arginine decarboxylase (*L*-ADC) antibody on the pharmacological actions of morphine** *L*-ADC is the synthase of agmatine. If we managed to inhibit the *L*-ADC activity using *L*-ADC antibody, the synthesis of endogenous agmatine might decrease. In mouse heat radiation tail flick assay and mouse 55 °C hot plate test, *L*-ADC antibody inhibited morphine analgesia in a concentration-dependent manner, 1:10 diluted *L*-ADC antibody (icv) reduced the PMAP of morphine 5 mg/kg by about 37 % and 38 % in the two animal models, respectively. *L*-ADC antibody promoted the development of morphine tolerance. Co-administration of *L*-ADC antibody (1:1000-1:10 diluted, icv) further reduced the PMAP of morphine 5 mg/kg by about 57 % and 40 % in these two models compared with morphine-treated mice, respectively[13].

**Influence of DFMO or AMG on the pharmacological actions of morphine** Difluomethylornithine (DFMO) is the inhibitor of ornithine decarboxylase. Through the inhibition of *L*-arginine degradation by the ornithine route, DFMO might increase the quantity of endogenous agmatine. Aminoguanidine (AMG) is the inhibitor of diamine oxidase. It might also increase the concentration of endogenous agmatine through the inhibition of the enzyme. So both DFMO and AMG might exert the same effects as exogenous agmatine[14].

DFMO and AMG have a weak analgesic effect. In the acetic acid writhing test, writhing number was about 23 times for control mice within the period of 15 min after administration of 0.6 % acetic acid (ip). DFMO

(0.5 mg/kg, icv) or AMG (0.25 mg/kg, icv) decreased the writhing number to 8.7 and 7.5 times, respectively. These effects may be mediated through imidazoline receptors because the effects could be antagonized by idazoxan. In heat radiation tail-flick assay, AMG (0.25 mg/kg, icv) also increased the pain threshold, the tail flick latency was increased from 3.0 s to 4.9 s[14].

DFMO and AMG enhanced morphine analgesia. In mouse acetic acid writhing test, morphine 0.5 mg/kg reduced the writhing number to 10 times, co-administration of DFMO (0.125 mg/kg, icv) plus morphine further reduced the writhing number to 4.9 times. In mouse heat radiation tail-flick assay, DFMO (0.5 mg/kg, icv) increased the PMAP of morphine 2.5 mg/kg from 48 % to 78 %. In mouse 55 °C hot plate test, DFMO (0.25 mg/kg, icv) increased the PMAP of morphine 5 mg/kg by about 30 %. In mouse heat radiation tail flick assay, AMG enhanced morphine analgesia, the PMAP of morphine 2.5 mg/kg was increased by about 25 %[14].

In heat radiation tail-flick assay, single dose of morphine (100 mg/kg, sc) induced acute tolerance indicated by the decrease in analgesic effect of morphine 5 mg/kg . The PMAP of morphine 5 mg/kg was reduced from 42 % to 16 %. DFMO (0.25 mg/kg, icv) or AMG (0.125 mg/kg, icv) inhibited the development of tolerance to morphine, in these groups, the PMAP of morphine 5 mg/kg was not changed before and after the pretreatment with large dose of morphine[14].

**Influence of chronic morphine treatment on the binding characteristics of I-R** After chronic morphine (10-80 mg/kg, sc) treatment for 16 d, the $B_{max}$ of [$^3$H]idazoxan binding sites was decreased by 44.3 % and 53 % in forebrain and cerebellum, respectively. On the other hand, the binding affinity indicated by $K_d$ value of [$^3$H]idazoxan binding was increased for about 48.4 % and 58.6 % in the two brain regions, respectively. These results inferred the possible cross talk between the opioid receptor system and imidazoline receptor system[15].

In conclusion, exogenous agmatine had a weak analgesic effect, enhanced morphine analgesia and inhibited tolerance to and dependence on morphine. The mechanisms were related to activation of imidazoline receptors, inhibition of calcium channel and NMDA receptor activity. By these mechanisms, agmatine inhibited the adaptation processes at different levels induced by opioids. When the concentration of endogenous agmatine was changed, the pharmacological actions of opioids were also influenced, inferring the possible modulatoty effect of endogenous agmatine on opioid functions. Endogenous agmatine and imidazoline receptors might be a new endogenous opioid modulation system. Agmatine is a typical opioid function modulator.

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