

Exploring the possible mechanisms of action behind the antinociceptive activity of *Bacopa monniera*

Manju Bhaskar, A. G. Jagtap

Department of Pharmacology, Bombay College of Pharmacy, Kalina, Santacruz (E), Mumbai, Maharashtra, India

ABSTRACT

Aim: Earlier studies have demonstrated that *Bacopa monniera* (BM), a plant described in Ayurveda for many CNS actions was found to exhibit antidepressant (methanolic extract at 20mg/kg and 40mg/kg p.o.) as well as antinociceptive activity (aqueous extract (AE) at 80 mg/kg, 120 mg/kg and 160 mg/kg p.o.). The present study sought to explore the possible mechanisms of antinociceptive effects of aqueous extract of *Bacopa monniera* (AEBM) at 80 mg/kg, 120 mg/kg and 160 mg/kg given orally. **Materials and Methods:** AEBM was given singly as well as with selective α_2 receptor blocker Yohimbine, selective β_1 receptor blocker Atenolol, serotonin receptor antagonist Cyproheptadine and a non-selective opioid receptor antagonist naloxone in experimental groups of mice and rats under strict protocols and conditions. **Results:** We observed that the antinociceptive effects of AEBM in the acetic acid writhing test was prevented by prior treatment with the selective Yohimbine (1 mg/kg, i.p; 14.50 ± 2.26 and 37.17 ± 2.14 writhes in the AEBM-treated and yohimbine pre-treated AEBM groups, respectively) and selective β_1 Atenolol receptor blocker (1 mg/kg, i.p; 14.50 ± 2.26 and 31.00 ± 5.44 writhes in the AEBM-treated and yohimbine pre-treated AEBM groups, respectively). In the formalin test, the reduction in licking time with AEBM was found to be reversed by prior treatment with serotonin receptor antagonist Cyproheptadine (1 mg/kg, i.p; 47.33 ± 2.25 s and 113.50 ± 3.83 s (during phase I i.e. 0-5 min) and 26.67 ± 3.83 s and 88.17 ± 7.27 s (during phase II i.e. 20-30 min) in the AEBM-treated and Cyproheptadine pre-treated AEBM groups, respectively). The % increase in tail flick latency with AEBM was prevented by prior treatment with the non-selective opioid receptor antagonist naloxone (2mg/kg, i.p; 282.35 and 107.35 in the AEBM-treated and naloxone-treated groups, respectively). **Conclusions:** Our results indicate, that the endogenous adrenergic, serotonergic and opioidergic systems are involved in the analgesic mechanism of action of the aqueous extract of *Bacopa monniera*.

Key words: Analgesic activity, *Bacopa monniera*, formalin test, tail immersion test, writhing test

INTRODUCTION

Pain is a complex neurobiological phenomenon, with a diversity of neurochemical factors contributing to both peripheral and central pain-signalling mechanisms.

Address for correspondence:

Dr. A.G. Jagtap,
Department of Pharmacology, Bombay College of Pharmacy,
Kalina, Santacruz (E), Mumbai - 400 098, Maharashtra, India
E-mail: jagtaparti@gmail.com

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Antidepressant agents are often used in the treatment of pain and may bring about their beneficial actions through a number of mechanisms.^[1] Antinociceptive effects can be enhanced by blocking 5-hydroxytryptamine 1A receptors, i.e. 5-HT_{1A} receptors (which have a pronociceptive influence), similar to the antidepressant activity.^[2] Antidepressants have significant pharmacological actions at crucial areas and nuclei involved in this circuit, such as the locus coeruleus nucleus, the dorsal and magnus nuclei in the raphe and the dorsal horn of the spinal cord. Thus, antidepressants can facilitate the endogenous pain control system acting at this neuroanatomical level^[3] resulting in an increase in nociceptive threshold. Animal studies performed with single administration of antidepressant drugs in acute pain models of pain reaction, hot-plate test, tail flick test and chemical test of sub chronic pain, formalin test and writhing test, confirm that antidepressant drugs have analgesic properties.

The increased availability of Noradrenaline (NA) and 5-Hydroxytryptamine (5-HT) in the synaptic cleft is the main,

but not the only possible mechanism of the analgesic action of antidepressants. Such action would result from inhibition of reuptake of these two monoamines by blockade of their specific transporters in the presynaptic membrane. NA and 5-HT receptors are greatly involved in regulating nociceptive sensation at different levels in nervous system. In this regard, antidepressants seem to enhance endogenous pain control and are considered to increase or maintain the activity of the descending inhibitory bulbospinal pathway, which is compromised in chronic pain conditions.^[3]

Bacopa monniera (syn. *Herpestis monniera* L.; Scrophulariaceae) is a commonly used *Ayurvedic* drug for mental disorders.^[4] It has been reported to exert several neuropsychopharmacological actions including anxiolytic,^[5] antidepressant,^[4] anticonvulsive,^[6] antioxidant activity and antinociceptive activity.^[7] In the present study, we investigated the possible mechanism of action behind the antinociceptive action of aqueous extract of *Bacopa monniera*.

MATERIALS AND METHODS

Animals

Swiss albino mice of either sex weighing 20-25g, and adult Wistar rats of either sex weighing 180-250g, were used. The animals were maintained in standard laboratory conditions with food and water *ad libitum*, under a 12 hour light/12 hour dark cycle. The experiment was conducted between 10:00 and 17:00 hours. The experimental protocols were approved by IAEC (Institutional Animal Ethics Committee) of Bombay College of Pharmacy.

Drugs

The following drugs were obtained from the companies as gift samples: atenolol (Ariane Orgachem, Aurangabad), yohimbine hydrochloride (Manus Aktteva, Ahemdabad), cyproheptadine hydrochloride tablets (Ciplactin, Cipla) and naloxone hydrochloride injections (Nex, Neon Labs). The aqueous extract of *Bacopa monniera* (AEBM) was a gift sample from Ayurchem Products, Mumbai. The specifications of AEBM extracts were 87.20% solubility in water and 83.20% solubility in 50% v/v alcohol, 20.70% saponins as bacosides and 5.56% and 4.93%, total ash and moisture content values, respectively, as per the Brahmi extract in-house specifications of Ayurchem Products. AEBM was administered after reconstitution of the dried powder extract with water. All other drug substances were dissolved in saline solution.

Mechanism studies' for involvement of different receptors in analgesic activity of antidepressants

Involvement of α_2 and β_1 adrenergic receptors in analgesic activity in Acetic acid induced writhing test in mice^[8-11]

In acetic acid induced abdominal writhing test, injection of

irritants like acetic acid into the peritoneal cavity induces pain. It produces steady and prolonged pain associated with tissue damage and also involves more movements and postural adjustments of the abdominal portion and rest of the body. The selective adrenergic receptor blockers incorporated in the study were atenolol (β_1) and yohimbine (α_2). They were selected, since yohimbine reversed the spinal component of morphine antinociception,^[12] and atenolol inhibited the analgesic effects of desipramine and nortriptyline in acetic acid induced writhing test.^[13]

Swiss albino mice were divided into thirteen groups [Table 1] of six mice each. Food and water were provided *ad libitum* to the animals.

Involvement of 5-HT Receptors in Analgesic Activity in Formalin Test in Rats^[7,14,15]

Formalin test is a well known chronic pain model of chemically induced nociception. The intraplantar injection of dilute formaldehyde causes a biphasic pain related behaviour initiated by direct stimulation of nociceptors, leading to activation of C fibres. This first phase lasts for a few minutes and reflects the neurogenic component of nociception, being reduced mainly by opioid-like drugs. It lasts only for a few minutes and is believed to be driven by primary afferent nociceptor activity. The inflammatory component of nociceptive response (second phase) starts after a silent period of 10-15 minutes and

Table 1: Experimental groups for writhing test with the Swiss albino mice divided into 13 groups with 6 mice in each group

Group	Treatment	Dose
1	Vehicle control	0.9% saline 10 mg/kg intraperitoneally (i.p.)
2	Yohimbine	1 mg/kg (i.p.)
3	Atenolol	1 mg/kg (i.p.)
4	Vehicle control	Distilled water 10 mg/kg per oral (p.o.)
5	AEBM	80 mg/kg (p.o.)
6	AEBM	120 mg/kg (p.o.)
7	AEBM	160 mg/kg (p.o.)
8	Yohimbine + AEBM	Yohimbine (1mg/kg, i.p) + AEBM (80 mg/kg p.o)
9	Yohimbine + AEBM	Yohimbine (1mg/kg, i.p) + AEBM (120 mg/kg p.o)
10	Yohimbine + AEBM	Yohimbine (1mg/kg, i.p) + AEBM (160 mg/kg p.o)
11	Atenolol + AEBM	Atenolol (1mg/kg, i.p) + AEBM (80 mg/kg p.o)
12	Atenolol + AEBM	Atenolol (1mg/kg, i.p) + AE BM (120 mg/kg p.o)
13	Atenolol + AEBM	Atenolol (1mg/kg, i.p) + AEBM (160 mg/kg p.o)

Mice received an intraperitoneal (i.p.) injection of acetic acid (AA) (0.6% solution, 10 mg/kg), 30 minutes after all drug administration. Mice were observed, in separate individual chambers, for manifestation of abdominal writhes, which were recorded over a period of 20 minutes.

lasts for 60 minutes, and is thought to arise from nociceptive spinal neuronal hyperactivity. It is mediated by the release of mediators such as bradykinin, histamine, sympathomimetic amines, tumor necrosis factor and interleukins. Phase 2 is inhibited by cyclooxygenase inhibitors. Drugs that act primarily as central analgesics inhibit both the phases while peripherally acting drugs inhibit only the phase 2.

Wistar rats were divided into nine groups of six rats each as shown in Table 2. Food and water were provided *ad libitum* to the animals.

Involvement of opioid receptor in analgesic activity in Tail immersion test^(16,17)

Tail immersion test has been developed to be selective for morphine- like compounds. Tail flick is a spinally mediated reflex to nociceptive stimuli. The fast rising pain in the tail gives rise to rapid tail flick and rapid tail withdrawal at the lowest possible threshold. Swiss albino mice were divided into nine groups of six mice each as shown in Table 3. Food and water were provided *ad libitum* to the animals.

Statistical analysis

All results are expressed as the mean ± Standard Deviation (SD). Statistical evaluation of the data was performed using one-way analysis of variance followed by Dunnett’s test. The minimum level of significance considered was *P* < 0.05.

RESULTS

As shown in Table 4, prior to treatment with Yohimbine (1 mg/kg) and Atenolol (1 mg/kg) fully prevented the antinociceptive

effects of AEBM (120 mg/kg and 160 mg/kg). Specifically, whereas the control mice treated with vehicle displayed 35.50 ± 1.52 writhes, pretreatment with yohimbine increased abdominal constrictions in AEBM (120 mg/kg) - treated mice from 25.00 ± 4.00 to 34.67 ± 2.66 writhes and in AEBM

Table 3: Experimental groups for tail immersion test with the Swiss albino mice divided into 9 groups as shown in table with 6 mice in each group

Group	Treatment	Dose
1	Vehicle control	0.9% saline 10 mg/kg intraperitoneally (i.p.)
2	Naloxone	2 mg/kg (i.p.)
3	Vehicle control	Distilled water 10 mg/kg per oral (p.o.)
4	AEBM	80 mg/kg (p.o.)
5	AEBM	120 mg/kg (p.o.)
6	AEBM	160 mg/kg (p.o.)
7	Naloxone + AEBM	Naloxone (1mg/kg, i.p) + AEBM (80 mg/kg p.o)
8	Naloxone + AEBM	Naloxone (1mg/kg, i.p) + AEBM (120 mg/kg p.o)
9	Naloxone + AEBM	Naloxone (1mg/kg, i.p) + AEBM (160 mg/kg p.o)

The tail flick latency time was observed in all mice at 0, 30, 60, 120, 180 and 240 minutes.

Table 4: Involvement of α₂ and β₁ adrenergic receptor in analgesic activity-effect of yohimbine and atenolol on aqueous extract of *Bacopa monniera* in acetic- acid induced writhing test in mice

Treatment (mg/kg)	No. of Writhes in 20 min (Mean ± SD)	Percentage (%) protection
Vehicle Control (10mg/kg, i.p.)	36.83 ± 1.72	-----
Yohimbine (1mg/kg, i.p)	34.67 ± 2.16	5.87
Atenolol (1mg/kg, i.p)	41.83 ± 5.19	-13.57
Vehicle Control (10 mg/kg, i.p.)	35.50 ± 1.52	-----
AEBM (80 mg/kg p.o)	36.17 ± 2.64	-1.88
AEBM (120 mg/kg p.o)	25.00 ± 4.00**	29.57
AEBM (160 mg/kg p.o)	14.50 ± 2.26**	59.15
Yohimbine (1mg/kg, i.p) + AEBM (80 mg/kg p.o)	37.00 ± 1.55	-4.22
Yohimbine (1mg/kg, i.p) + AEBM (120 mg/kg p.o)	34.67 ± 2.66	2.33
Yohimbine (1mg/kg, i.p) + AEBM (160 mg/kg p.o)	37.17 ± 2.14	-4.70
Atenolol (1mg/kg, i.p) + AEBM (80 mg/kg p.o)	39.17 ± 0.98	-10.33
Atenolol (1mg/kg, i.p) + AEBM (120 mg/kg p.o)	33.17 ± 5.19	6.56
Atenolol (1mg/kg, i.p) + AEBM (160 mg/kg p.o)	31.00 ± 5.44	12.67

Data presented as mean ± SD n=6; ANOVA followed by Dunnett’s test ***P*<0.01 compared to the control group

Table 2: Experimental groups for formalin test with the Wistar rats mice divided into 9 groups with 6 mice in each group

Group	Treatment	Dose
1	Vehicle control	0.9% saline 10 mg/kg intraperitoneally (i.p.)
2	Cyproheptadine	1 mg/kg (i.p.)
3	Vehicle control	Distilled water 10 mg/kg per oral (p.o.)
4	AEBM	80 mg/kg (p.o.)
5	AEBM	120 mg/kg (p.o.)
6	AEBM	160 mg/kg (p.o.)
7	Cyproheptadine + AEBM	Cyproheptadine (1mg/kg, i.p) + AEBM (80 mg/kg p.o)
8	Cyproheptadine + AEBM	Cyproheptadine (1mg/kg, i.p) + AEBM (120 mg/kg p.o)
9	Cyproheptadine + AEBM	Cyproheptadine (1mg/kg, i.p) + AEBM (160 mg/kg p.o)

One hour later, the rats were injected with 0.05 ml of 10% formalin in the dorsal surface of the right hind paw intraplantarly. The time the animal spent licking the injected paw was recorded in two phases: First 5 minutes after formalin injection (first phase, neurogenic pain response) and 20–30 minutes after formalin injection (second phase, inflammatory pain response).

(160 mg/kg)- treated mice from 14.50 ± 2.26 to 37.17 ± 2.14 writhes. In case of Atenolol, pretreatment increased abdominal constrictions in AEBM (120 mg/kg)-treated mice from 25.00 ± 4.00 to 33.17 ± 5.19 writhes and in AEBM (160 mg/kg)-treated mice from 14.50 ± 4.00 to 31.00 ± 5.44 writhes.

As shown in Table 5, prior treatment with Cyproheptadine (1 mg/kg) fully prevented the antinociceptive effects of AEBM (120 mg/kg and 160 mg/kg). The control rats treated with vehicle displayed the licking time of 128.00 ± 3.63 s (0-5 mins) and 119.33 ± 2.94 s (20-30 mins). Pretreatment with cyproheptadine increased the licking time in AEBM (160 mg/kg)-treated group from 47.33 ± 2.25 s to 113.50 ± 3.83 (0-5 mins) and from 26.67 ± 3.83 s to 88.17 ± 7.27 s (20-30 min). The prevention of

antinociceptive effects after pretreatment with Cyproheptadine as observed with AEBM (160 mg/kg) was significant to those observed with AEBM (80 mg/kg and 120 mg/kg).

Involvement of opioid receptor in analgesic activity in Tail immersion test in mice is presented in Table 6. As shown in the Table, prior treatment with Naloxone (2 mg/kg) fully prevented the antinociceptive effects of AEBM (120 mg/kg and 160 mg/kg). At 120 minutes, the % increase in tail flick latency in AEBM (120 mg/kg) and AEBM (160 mg/kg) was found to be higher than the control animals. Pretreatment with naloxone (2 mg/kg) significantly decreased the % increase in tail flick latencies from 282.35 and 107.35 with AEBM (160 mg/kg). The prevention of antinociceptive effects after pretreatment with Naloxone as observed with AEBM (160 mg/kg) was significant to those observed with AEBM (80 mg/kg and 120 mg/kg).

Table 5: Involvement of 5-hydroxytryptamine receptor in analgesic activity – effect of Cyproheptadine on aqueous extract of *Bacopa monniera* in Formalin test in rats

Treatment (mg/kg)	Licking time (s) (Mean ± SD)	
	0-5 min	20-30 min
Vehicle Control (i.p)	134 ± 3.40	123 ± 7.98
Cyproheptadine (1 mg/kg, i.p)	127.33 ± 1.86	119.33 ± 2.94**
Vehicle Control (p.o)	128.00 ± 3.63	86.33 ± 2.25
AEBM (80 mg/kg p.o)	62.17 ± 2.60**	33.33 ± 1.50**
AEBM (120 mg/kg p.o)	50.17 ± 2.13**	32.00 ± 2.85**
AEBM (160 mg/kg p.o)	47.33 ± 2.25**	26.67 ± 3.83**
Cyproheptadine (1 mg/kg, i.p) + AEBM (80 mg/kg p.o)	105.33 ± 9.17**	69.50 ± 3.51**
Cyproheptadine (1 mg/kg, i.p) + AEBM (120 mg/kg p.o)	109.67 ± 5.05**	71.00 ± 6.51**
Cyproheptadine (1mg/kg, i.p) + AEBM (160 mg/kg p.o)	113.50 ± 3.83**	88.17 ± 7.27**

Data presented as mean ± SD n=6; ANOVA followed by Dunnett's test, **P<0.01 compared to the control group

DISCUSSION

The involvement of monoamines, mainly serotonin and noradrenaline, in the physiological control of nociception has been well established.^[15] α -adrenoceptor subtypes are distributed both spinally and supraspinally. In the abdominal constriction assay, α_2 rather than α_1 -adrenoceptors appear to play an integral role in antidepressant induced antinociception. Pharmacological and autoradiographic studies have demonstrated that opioid and α_2 -adrenoceptors are co-localized within the same laminae of the dorsal horn further suggesting a possibility of an opioid-adrenoceptor interaction at the spinal level.^[18] In the abdominal constriction assay, since yohimbine produced a decrement in the protective action of AEBM, indicating the probable involvement of α_2 -adrenoceptors in the analgesic action of AEBM. The β -adrenergic receptors participate in the mechanism of action of antidepressants, a hypothesis that was first proposed by

Table 6: Involvement of opioid receptors in analgesic activity- effect of Naloxone on aqueous extract of *Bacopa monniera* in Tail immersion test in mice

Treatment (mg/kg)	0 minute	30 minutes	60 minutes	120 minutes	180 minutes	240 minutes
	Latency time (sec)	% increase in latency	% increase in latency	% increase in latency	% increase in latency	% increase in latency
Vehicle Control (i.p)	0.69±0.22	-----	-----	-----	-----	-----
Naloxone(2 mg/kg i.p)	0.76±0.11	49.20	125.00	163.23	62.65	37.63
Vehicle Control (p.o)	0.69±0.21	-----	-----	-----	-----	-----
AEBM (80 mg/kg p.o)	1.12±0.02**	190.47**	164.86**	210.29**	91.25**	43.47**
AEBM (120 mg/kg p.o)	1.16±0.02**	176.19**	167.56**	216.17**	98.75*	60.86
AEBM (160 mg/kg p.o)	1.18 ± 0.03**	182.53**	233.78**	282.35**	220.00**	154.34**
Naloxone (2 mg/kg i.p) + AEBM (80 mg/kg p.o)	1.15±0.07**	95.23**	67.56**	88.23**	68.75**	35.86*
Naloxone (2 mg/kg i.p) + AEBM (120 mg/kg p.o)	1.25±0.06**	134.92**	64.86*	63.23*	32.50*	-48.91**
Naloxone (2 mg/kg i.p) + AEBM (160 mg/kg p.o)	1.35±0.10**	158.73**	106.75*	107.35**	27.50	-61.95**

Data presented as mean ± SD n=6; ANOVA followed by Dunnett's test, ** P< 0.01 compared to the control group, *P< 0.05 compared to the control group

Vetulani *et al.*^[19] These receptors are located in areas directly related to pain pathways.^[20] β -adrenergic receptors are closely related to two neural systems that are directly implicated in pain modulation, i.e. serotonergic^[21] and opioid,^[22] which in turn, participate in the mechanism of action of antidepressants. In the abdominal constriction assay, β_1 -receptors seem to play a role in analgesic activity since atenolol produced a decrement in the protective action of AEBM.

The neurotransmitter 5-hydroxytryptamine (5-HT) is widely accepted as an important participant in the brain and spinal inhibition of nociceptive transmission.^[23] Behavioural studies have demonstrated that 5-HT is implicated in the control exerted by the brain on the nociception either by afferent fibre hyperpolarization or through presynaptic action. The destruction of serotonergic projection affects nociception. Serotonergic deficiency is a common factor in both mental depression and chronic pain.^[24] The increasing availability of 5-HT at the synapse is reported to inhibit nociception by acting at the spinal cord, brainstem or thalamic levels. 5-HT₁ and 5-HT₂ receptors are involved in the fluoxetine-induced antinociception in diabetic mice.^[25] We studied the involvement of 5-HT receptors in analgesic activity of AEBM, by using 5-HT₂ receptor antagonist cyproheptadine. Cyproheptadine antagonizes 5-HT receptors in the Central Nervous System (CNS) and the periphery, in addition to its antihistaminic action.^[26] AEBM showed an increase in the licking time in presence of cyproheptadine. The analgesic effect was found to be dose related for AEBM. The difference in licking time values in the early and late phase indicate the involvement of 5-HT receptors in analgesic activity of AEBM.

Naloxone hydrochloride and Naltrexone hydrochloride in lower dose have been reported to be effective antagonists of opioid analgesia in Acetic acid induced writhing.^[27] This suggests a complex mechanism underlying the antinociceptive effect of antidepressants. Opioids reduce the sensory discriminative component of pain^[28] and antidepressants produce analgesia by potentiating the pain modulating system rather than having a direct synaptic effect.^[29] Opiates enhance serotonergic activity in the brain by increasing the turnover rate of serotonin, without altering overall concentration of neurotransmitter,^[30] through an indirect action via inhibition of gamma-amino-butyric acid (GABA)-containing neurons in the dorsal raphe nuclei and also by increasing 5-HT turnover at the spinal cord level.^[31] In the present study increase in latency was found to reduce with time for the groups administered AEBM in combination with the antagonist, thereby indicating the involvement of opioid receptors in analgesic activity. A possible explanation for antagonism displayed by naloxone is that it blocks the release of some opioid peptides which interact as agonists at both μ and δ opioid receptors to inhibit nociceptive transmission.^[31]

The percentage increase in latency reduced from 1 hour onwards

till 3 hours. The reduction at 0.5 hours was not significant. After 3 hours, the reduction remained constant at 4 and 6 hours. In the presence of opioid receptor antagonist naloxone there was a reduction in percentage protection offered by AEBM (160 mg/kg) and thereby an antagonistic effect was observed.

CONCLUSIONS

When AEBM was given in combination with atenolol (β_1 -adrenergic receptor antagonist) and with yohimbine (α_2 -adrenergic receptor antagonist), its analgesic activity was reversed indicating the involvement of β_1 -adrenergic and α_2 -adrenergic receptors in its analgesic activity. Similarly cyproheptadine also reversed analgesia, thereby indicating the involvement of 5-HT receptors in analgesic activity. AEBM, when given in combination with naloxone did not increase the latency for analgesic effect. Therefore their analgesic effect is antagonized by naloxone, which indicates involvement of opioid receptors in analgesic activity.

Thus, aqueous extract of *Bacopa monniera* (AEBM) exhibited analgesic activity in both acute and chronic pain conditions. The results provide evidence AEBM exhibits analgesic activity through multiple pain pathways like serotonergic, noradrenergic and opioidergic systems. Further isolation and purification of the crude aqueous extract may lead to compounds with potential analgesic activity.

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