European Review for Medical and Pharmacological Sciences 2013; 17: 2019-2022

Involvement of monoaminergic system in the antidepressant-like effect of aqueous extract of *Channa striatus* in mice

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Abstract. – BACKGROUND: In our previous study, the aqueous extract of *Channa striatus* (family: Channidae) fillet (AECSF) showed an antidepressant-like effect in mice. However, the mechanism of the antidepressant-like effect is unknown.

AIM: The objective of this study was to explore the involvement of monoamines in the antidepressant-like effect of AECSF in mice.

MATERIALS AND METHODS: AECSF was prepared by steaming the fillets of *C. striatus*. The male ICR mice were pretreated with various monoaminergic antagonists viz., *p*-chlorophenylalanine (100 mg/kg, i.p.), prazosin (1 mg/kg, i.p.) and yohimbine (1 mg/kg, i.p.), SCH23390 (0.05 mg/kg, s.c.) and sulpiride (50 mg/kg, i.p.) followed by treatment with AECSF and tested in tail suspension test (TST). Two-way ANOVA with Tukey test were used at $p < 0.05$ for significance.

RESULTS: The pretreatments with *p*-chlorophenylalanine, prazosin and yohimbine, but not with SCH23390 and sulpiride, were able to reverse the antidepressant-like effect of AECSF in TST.

CONCLUSIONS: The antidepressant-like effect of AECSF may be mediated through the serotonergic and noradrenergic systems and not through the dopaminergic system.

Key Words:
Channa striatus, Tail suspension test, Serotonin, Noradrenaline, Dopamine.

Introduction

Depression affects the mood, impairs the quality of life and work performance significantly[1]. Growing evidence suggests that nutritional supplements can be useful in treating major depressive disorder[2]. *Channa (C.) striatus* (Channidae), called as Haruan in Malay, is a fresh water snake-head fish found in Malaysia[3]. *C. striatus* exhibited antinociception effect[4] and antidepressant-like effect[5] in rodents in previous studies from our group. In continuation, this study was designed to explore the mechanism of antidepressant-like effect in mice.

Materials and Methods

Preparation of Aqueous Extract of C. Striatus Fillets (AECSF)

Aqueous extract of *C. striatus* fillets (AECSF) was prepared based on previously described method[4,5]. The resultant final concentration of the extract was 50% w/v (the weight refers to wet fish weight).

Animals

Male ICR mice (25-30 g) were obtained from Animal House, Faculty of Medicine and Health Sciences, University Putra Malaysia (UPM). All the animals used in this study were cared for and treated in accordance with the protocols specified by the the "Principles of Laboratory Animal Care" (NIH Publication No. 85-23, revised in 1985). All the study protocols were approved by the Animal Care and Use Committee, UPM. The animals were randomly assigned to different groups for the experiments (n = 6).

Drugs and Treatment

The drugs used were: *p*-chlorophenylalanine methyl ester (PCPA), prazosin, yohimbine, (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390), sulpiride and fluoxetine (all from Sigma Chemical Company, St. Louis, MO, USA). All drugs were administered by intraperitoneal (i.p.) route at the dose of 10 ml/kg body weight, except SCH23390 that was administered

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by subcutaneous (s.c.) route. Drugs were dissolved in normal saline except sulpiride that was diluted in saline with 5% dimethylsulfoxide (DMSO). Control animals received appropriate vehicle at the dose of 10 ml/kg. From our preliminary study[6], the lowest effective dose of AECSF was found to be 20% w/v and this dose is used in the mechanism study. The AECSF (50% w/v) was diluted with normal saline to 20% w/v and given at the dosage of 10 ml/kg body weight.

In order to assess the role of serotonergic system, animals were pretreated with PCPA (100 mg/kg/day, i.p., an inhibitor of serotonin synthesis) or vehicle, once a day, for 4 consecutive days[7]. Then, 24 h after the last PCPA or saline injection, animals were acutely treated with the AECSF (20% w/v at 10 ml/kg, i.p.), fluoxetine (10 mg/kg, i.p.) or vehicle and were tested in the tail suspension test (TST) 30 min later[8].

In order to assess the role of noradrenergic and dopaminergic systems, independent groups of animals were pretreated with vehicle (10 ml/kg, i.p.) or prazosin (1 mg/kg, i.p., α_1 antagonist) or yohimbine (1 mg/kg, i.p., α_2 antagonist) or SCH23390 (0.05 mg/kg, s.c., D_1 antagonist) or sulpiride (50 mg/kg, i.p., D_2 antagonist) separately. After 30 min, animals received AECSF (20% w/v at 10 ml/kg, i.p.) or vehicle and were tested in TST 30 min later[8].

Tail Suspension Test (TST)

Mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. After 2-3 min of vigorous struggling movements, the mice showed alternating periods of immobility and vigorous struggling[9]. The total duration of immobility was recorded during 6 min period with the help of a stop-watch[5].

Statistical Analysis

Results were expressed as mean ± SEM. Data were analyzed by two-way ANOVA test followed by Tukey's multiple comparison test as the *post hoc* test. Effects were considered as significant at $p < 0.05$.

Results

Statistical tests showed that the PCPA pretreatment significantly prevented the decrease in immobility time induced by either AECSF ($p < 0.05$) or fluoxetine ($p < 0.001$) treatment when compared to their respective treated groups (either AECSF or fluoxetine treated groups with vehicle pretreatment respectively) (Panel A, Figure 1). The pretreatment with prazosin ($p < 0.001$) and yohimbine ($p < 0.01$) significantly prevented the decrease in immobility time induced by AECSF treatment in TST when compared with the group treated with AECSF after pretreatment with vehicle (Panel B, Figure 1). The two-way ANOVA test showed no significant effects of pretreatment (vehicle or SCH23390 or sulpiride) (Panel C, Figure 1).

Discussion

Involvement of Monoamines in the Antidepressant-Like Effect of AECSF

The pathophysiology of depression is linked to the deficiency of one or more monoamines in affected persons[10]. Antidepressants show their effects by regulating synaptic levels of one or more monoamines[10]. Hence, this study explored the impact of monoaminergic antagonists on the antidepressant-like effect of the AECSF. The lowest effective dose of AECSF in TST was 20% w/v at 10 ml/kg[6]. TST was used as the test in mechanism study due to its increased sensitivity[11].

Involvement of Serotonergic System

Several studies had established the role of serotonin in depression[10]. In our study, PCPA was used to inhibit the tryptophan hydroxylase, which catalyses the synthesis of serotonin[7]. PCPA administration (100 mg/kg/day, i.p.) for four consecutive days in mice was proved to deplete serotonin in rodents[7]. In our study, pretreatment with PCPA was able to significantly reverse the decrease in immobility time induced by AECSF. The PCPA pretreatment also significantly reversed the antidepressant-like effect of fluoxetine, which is similar to previous findings[8]. These findings suggest that serotonergic system plays a role in the antidepressant-like effect of AECSF.

Involvement of Noradrenergic System

Hypo function of the noradrenergic system was linked with depression[10]. Hence, adrenergic antagonists were used in our study to explore the involvement of noradrenergic system in the antidepressant-like effect of AECSF. The results showed that the pretreatments with prazosin (α_1-adrenoceptor antagonist) and yohimbine (α_2-adrenoceptor antagonist) respectively, were able

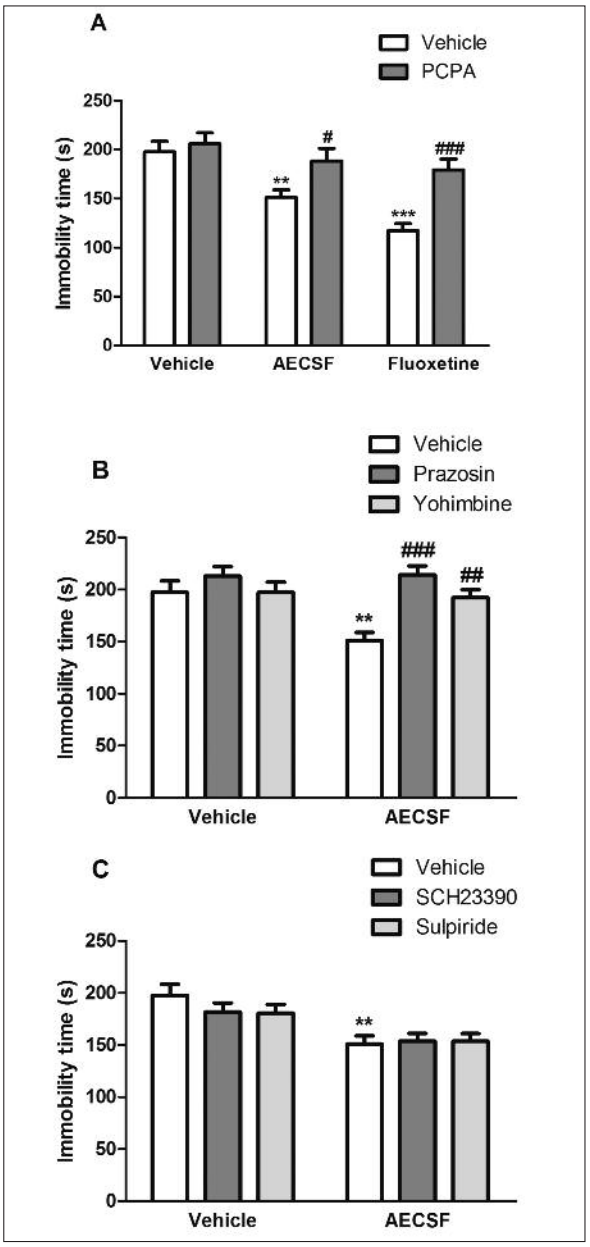

Figure 1. Effect of various pretreatments on the treatment with AECSF (20% w/v at 10 ml/kg i.p.) on the immobility time (seconds) in TST in male ICR mice. ***A,*** Effect of pretreatment with PCPA (100 mg/kg, i.p. for four consecutive days). ***B,*** Effect of pretreatment with prazosin (1 mg/kg, i.p.) and yohimbine (1 mg/kg, i.p.). ***C,*** Effect of pretreatment with SCH23390 (0.05 mg/kg, s.c.) and sulpiride (50 mg/kg, i.p.). Data represent the mean ± S.E.M. of 6 animals. $^{**}p < 0.01$, $^{***}p < 0.001$, when compared with the vehicle-treated. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ when compared with either AECSF or fluoxetine treated group alone.

to reverse the antidepressant-like effect of the AECSF indicating that the AECSF may exert its effect in the TST by interacting with α_1 and α_2-adrenoceptors.

Involvement of Dopaminergic System

The involvement of dopaminergic system is suggested in the pathophysiology of depression[12]. Hence, dopamine D_1 receptor antagonist (SCH23390) and D_2 receptor antagonist (sulpiride) were used to assess the involvement of dopaminergic system in the antidepressant-like effect of AECSF. The results indicated that the pretreatment with neither SCH23390 nor sulpiride produced any significant reversal of antidepressant-like effect induced by AECSF suggesting that the antidepressant-like effect may not be mediated through dopaminergic receptors.

Omega-3 fatty acids exhibited antidepressant effect in humans[13]. Oral treatment with L-lysine and L-arginine was reported to reduce anxiety and stress[14]. Treatment with yeast hydrolysate, which was found to contain high concentrations of glutamic acid and aspartic acid, was reported to exhibit anti-stress activity in humans[15]. AECSF was reported to contain all these fatty acids and amino acids[16]. Although the possible synergistic involvement of these fatty acids and amino acids might be anticipated in the observed antidepressant-like activity of AECSF, it cannot be concluded from this study. Further studies are required to identify the bioactive compounds.

Conclusions

The mechanism of antidepressant-like activity of AECSF in mice was found to be mediated through serotonergic and noradrenergic systems and not through dopaminergic system.

Acknowledgements

This research was financially supported by Research University Grant Schemes (RUGS No: 91140) by University Putra Malaysia, Selangor, Malaysia.

Conflict of Interest

None.

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