Ancient Science of Life Vol. No 17(3), January 1998 pages 169 - 181

ALTERATIONS IN THE SENSITIVITY OF 5TH RECEPTOR SUB-TYPES FOLLOWING CHRONIC ASVAGANDHA TREATMENT IN RATS

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Received: 12 July, 1997 **Accepted: 24 December, 1997**

Abstract: *Asvagandha (Withania somnifera) is an important antistress drug has now been sown to have an antidepressant action in clinically depressive patients, However, the mechanism of its antidepressant action has not been studied. Normal rats fed with asvagandha root extract (100mg/kg orally) for 4 and 8 weeks showed enhanced open field behavior and emotional stability along with a moderate but significant enhancement in the functional sensitivity of 5 HT2 receptors in the brain and a reciprocal subsensitivity of the 5HT1A receptors chronic asvagandha treatment (propylactically) was effective in preventing the behavioral deficit in open field activity in an animal model of depression. This was accompanied by an adaptive supersensitivity of the postsynaptic 5HT2 receptors in the brain. The effect of chronic Asvagandha on 5HT receptor subtypes is similar to the action of chronic ECT treatment and several antidepressant drugs.*

INTRODUCTION

Withania somnifera (Asvagandha) is one of t most valuable medicinal herbs1. Apart from its vast range of physiological effects[2] recent studies have strongly emphasized its beneficial effects as an adaptogenic, [3,6] anti-stress [3,6] and tonic agent. Asvagandha has been shown to reduce the incidence of aspirin and physical stress induced gastric ulcer. [5] more recently, the total root extracts of asvagandha have shown to exhibit antistress activity in widely different stress situation[3] similarly, it exhibited adaptogenic$_6$ and immunostimulatory activity, suggesting a high potential of this plant as stress lowering agent[6].

Chronic asvagandha has been found to exert an anxiolytic action, both in clinical [7,8,9] as well as animal studies[3].

Neurochemical studies have shown that chronic Asvagandha induces a depletion of acetylcholine and dopamine in the brain and increases whole brain level of histamine and serotonin.[10] Further, recent clinical trials have indicated a considerable therapeutic effect of Asvagandha in management of clinical depression. Biochemically major depression is characterized by a dysregulation of central biogenic amine neurotransmitter system (mainly serotonergic, noradrenergic and dopaminergic)[11] The serotonin (5HT)

hypothesis of depression has received special attention as 5T has been related to many of the major symptoms of depression eg, sleep, mood, activity and cognitive dysfunction.[12,13] Moreover the preclinical studies on the action of different types of antidepressant treatment on the serotonin system revealed, as a common effect, an enhancement of the 5HT neurotransmission.[13,14] Tricyclic antidepressants and electroconvulsive therapy enhance the sensitivity of the postsynaptic 5HT2 receptors to 5HT. %HT1A receptor agonists (effective antidepressant) produce the tonic activation of postsynaptic 5HT1A receptors. [14,15] Monoamine oxidase inhibitors enhance the availability of the releasable 5HT uptake blockers increase the efficacy of 5HT neurons by desensitizing the 5HT autoreceptors located on 5HT nerve terminals. [14,15].

Based on the above information, the present stud was designed to investigate the effect of longterm Asvaganda as a propyllactic antidepressant drug, on an well established animal model of depression[16]. And secondly, to assess the functional sensitivity of the 5HT1A and 5HT2 receptors following long term Asvaganda administration

Materials and Methods

Animal:- Adult male albino rats weighing 150-200 gm. Initially were maintained on an adlib rat pellet diet and tap water (unless mentioned otherwise) and 12 hr light: dark schedule. The were group housed (3-4 per cage) at a room temperature of 24 ± 25^{o}C.

Drug:- 500g Asvagandha plant root (dried and powdered) were extracted with alcohol to obtain a 50g extract. A 40% suspension was made in distilled water (pyrogen free) with the addition of 2% gum acacia powder.

8-OH Di (n-propyl amino tetraline), 5HT receptor agonist and 5-MeoDMT (5HT1/5HT2 agonist) was dissolved in 0.9% saline and freshly made before use.

Depression Model:- A slightly modified version of a stress based model developed by Kat et al (1982)15 was used. The animals were subjected to a variety of different stressors over a 3-week period (6 day/week). Stressors were administered once per day, between the firs and eight our of the light cycle to maximize the unpredictability on the nature of the stressors and time of delivery. A schedule of stressors is given in Tale 1.

Open field Test (OFT):- The apparatus consisted of a circular wooden arena (70cm in diameter, 30cm height) with a sunmica base with three concentric circles divided into 24 segments by radial lines originating from the centre, Each animal was tested individually for 3 min to observe their ambulation (number of squares crossed on the sunmica base), rearing activity (number of times animal stood on its hind limb with or without the support of the circular wall) and emotional fecal pellet exvretion[17].

Assessment of 5HT Receptor Sensitivity:-

(1a) 5HT1A Receptor:- 5HT1A postsynaptic receptor sensitivity was assessed by scoring the '5HT syndrome'[18] and 'hypothermia'[18] elicited by the specific 5 HTIA agonist 8-OH-DPAT. The syndrome was measured 48h after the last treatment (drug or stress) according to the method of Backus et al (1990)[19] For testing the 15ht syndrome', rats were placed in an observation arena for habituation , [5,6] min before agonist administration. Drug was injected 2 min before the first observation period and following components of the

sybdrome were scored; flat posture, fore paw treading, tremor, straub and tail scoring was done on a 4-point ranked intensity scale as follows:-

0=absent
1=equivocal
2=present
3=extreme

In case of 8-OHDPAt, scording was done in observation period of 45 sec per rat, after every 5 minutes, for 45 min. scores for each component ere summed up over all the observation periods scoring was done blindly with respect to the treatment given minimum four components out of five had to be present, in order to accept th5HT syndrome as present.

(2b) Hypothermia:- The rectal temperature of t eras were measured before the agonist injection by a thermister probe (yellow spring Co, U.S.A) inserted 5cm into the rectum. Te probe was connected to a 6-channel telethermometer apparatus (APLAB, India). The rectal temperature was again recorded 30 min after 8-OH-DPAT (0.75 mg/kg, JP) administration. [18]

(3) 5HT2 Postsynaptic Receptor;- Postsynaptic 5HT2 receptor function was assessed by the induction of wet dog sake response (WDS) by 5ht agonist 5 MeO-DMT (5mg/kg, IP) and quipazine (1mg/kg, IP)20 Rats were placed singly in an observation cage 5-6 minutes before the agonist administration. The number of WDS were counted (by direct observation) for 60 min and 40 min for 5MeO – DMT and quipazine respectively after agonist administration. 'Wet dog shake is characterized as rapid side-to side twitches of the lead and ear.[21]

Plan of stud:-

After bringing the animals form the central animal house, they were housed at the laboratory for at least one week before being used in experiments, before starting the experiment, all the rats were individually tested in the open field (OFT) and high plus maze test for assessing their initial emotional reactivity and exploratory behavior. Reactivity and exploratory behavior. Subsequently, the animals were assigned to one of the following groups:

(1) Normal control without drug (n=1)
(2) 4&8 week Asvagandha treated group (n=5)
(3) Depression group (n=5)
(4) Depression + Asvagandha (n=5)

In the drug treated control group Asvagandha extract (100mg/kg) were fed to the rats orally with a feeding tube for either 4 weeks (6 day/week) or for 8 weeks (6 day/week). In the depression group rats were subjected to the stress schedule for 8 weeks. In the depression + Asvagandha group, animal were administered with Asvagandha for 1 week and from the second week animals were subjected to the stress model along with chronic concurrent Asvagandha administration for 8 weeks. All the groups were tested in the open field after 4 weeks and 8 weeks. 5T receptor sensitivity were also assessed at the end of four week and 8 week.

Statistical Analysis:- The open field activity was analyzed by 2-wy ANOVA followed y students unpaired or paid t-test for inter or intragroup comparison respectively. Observer scores for behavioral syndrome were analyzed by Mann-whittney U-test. The wet dog shake response were analyzed by one –way ANOVA, followed by students unpaired t-test.

Results:-

In normal tats 4 week Asvagandha administration did not significantly change the behaviour of the animals in the OFT. However, 8 week treatment significantly increased the ambulation and rearing activity ($p<0.05$) (Table 2).

Table 3 shows that in the depression model, after 4 week stress, the rats sowed significant psychomotor retardation and inactivity as shown by a significant reduction in ambulation.

($p<0.01$) as well as rearing ($p<0.01$), wile pellet excretion was increased ($t= 2.9$ $p<0.05$) when compared to prestress level. After 8 week of stress, the rats showed further reduction in ambulation ($t= 4.8$, $p< 0.001$), rearing ($t = 4.42$, $p< 0.001$) and increase in pellet excretion as compared to prestress level. Moreover, the animals showed extreme hesitation towards exploration of the center of the open field and remained mostly huddled near the wall of the arena. Grooming activity was also not observed.

When Asvagandha was administered concurrently with stressors (prophylactically) after 4 week, there was a significant improvement of the deficits. However, still ambulation was 16% less than prestress level. At the end of 8 weeks Asvagandha treatment, the stress + drug group exhibited 180% higher ambulatory actually ($p<0.001$) and 500% higher rearing activity ($p<0.001$) as compared to the depression group (Table 3).

5HT1A Receptor Mediated Behavioural Syndrome:-

Table 4 shows that following 4 week Asvagandha treatment to normal rats, two components of the '5Ht syndrome' viz fore paw padding and flat posture showed a significantly diminished response ($P<0.05$, $P<0.05$ resp.). Further, the hypothermic effect of 5HT1A receptor agonist was significantly potentiated in normal drug treated animal as compared to control. Following 8 week Asvagandha administration to normal rats, out of five components of 5T syndrome, tremor and flat posture showed a significantly diminished response (p,0.01, $P<0.01$ resp) The degree of hypothermia induced by 8- OH-DPAt remained similar to that after 4 – week drug treatment .

Table 5 shows that in the behaviorally depressed group (8 – week stress) tremor and flat posture were slightly enhanced ($P<0.05$, $P<0.01$) while other components remained unaltered compared to the control group. Table 5 also shows that when Asvagandha was administered prophyllactically for 8 weeks, tremor and flat posture were decreased significantly ($P< 0.05$ both group respectively) compared to depression group. The effect of Asvagandha was essentially similar to its effect on normal rats.

5HT2 Receptor Mediated Syndrome:-

Table 6 shows that in normal 4 week drug fed rats the WDS response week drug fed rats the WDS response showed a tendency to increase. However, the following 8 weeks of Asvagandha feeding, 5MeO-DMT induced WDS was significantly enhanced ($P<0.05$). In the behaviourally depressed rats where as apparently no alteration in the WDS response both 5MeO-DMT 2 quipazine. When Asvagandha s administered orally (prophylactically) concurrent with stressors, there was a significant enhancement ($P<0.01$) in the WDS after 8 weeks which was also

confirmed with quipazine (5HR1/5HT12 agonist).

Discussion

Our data shows that normal rats treated with Asvagandha extract (for 8 weeks) exhibited less emotional reactivity and slightly heightened exploratory activity in the open field. 4 weeks Asvagandha treatment resulted in a significant diminution in the functional sensitivity of the 5HT1A postsynaptic receptors, as indicated by the reduced expression of '5HT syndrome'. Tis syndrome is the most consistently utilized model to assess the sensitivity of the 5HT1A neurons.[22] Behavioral studies also suggest that sensitivity of the 5HT1A receptors are decreased in brain stem region after long term (4-6 weeks) antidepressant therapy, [18,23]. Out data also indicate that the sensitivity of the postsynaptic 5HT2 receptors was moderately enhanced following administration of Asvagandha, both, after 4 and 8 weeks, as indicated by the enhanced WDS syndrome. WDS response has been shown to be mediated by the postsynaptic 5HT2 receptors [20, 24] and the neural substrat is located rostral to bnulbospinal serotonergic nerons.[24] Many of the popular antidepressant drugs [25,26] have also shown to enhance the behavioral responsiveness (WDS) of 5HT2 receptors following chronic administration animal models. Electrophysiological studies have shown that the sensitivity to iontophortically applied 5HT is significantly enhanced b treatment with tricycles and ECS. [27, 28]

Our finding with the animalmodel of depression (chronic stress model of Katz et al) confirms the previous observations with this model. [16,17] this model was particularly chosen mainly for the following reasons; fist this is one of models with highest overall validity,[29] since the effects observed in the model increased corticosterone level, a lack of reactivity to an acute stress, [16] suppression of open field activity and anhedonia 30,31 – are all central features of clinical depression. Secondly, it offered the opportunity to study the prophylactic effect of long term drug treatment. Results show that after 4 weeks of stress, the rats exhibited significant deficit in psychomotor activity and increases emotional defecation. However, the diminution of psychomotor activity and exploratory activity became more pronounced at the end of 8 week. In these animals alterations in 5HT1A receptor sensitivity was less clear, as only one component sowed enhanced response while majority of components remained unchanged, the sensitivity of the 5HT2 receptors was also unaltered in this model which confirm the earlier results.[32] Earlier studies have shown that 5HT synthesis and turnover were significantly decreased in several brain areas in this model of depression. [32] thus, an impaired 5HT function at the presynaptic level may be one of the major factors contributing to the behavioural deficit observed.

Finally, the most significant finding in the present study was the ability of 8-week asvagandha treatment in preventing (propylactically) the development of behavioural deficit in 100% of the animals tested in the OFT. Similar reversal of the open field behavior deficit have also been reported following chronic prophylactic treatment with imipramine, amitryptylene and ECT, [30,31] Also these animal exhibited a significant enhancement in the functional sensitivity of the 5HT2 receptors. Such adaptive supersensitivity of the 5HT2 receptors may have an important role in mediating the antidepressant effect of Asvagandha in this model by increasing the serotonergic neurotransmission. The proposition that a serotonergic component

dos have a primary role in mediating the antidepressant action is strengthened by the fact that drugs the primarily effect the 5HT system were able to reverse many of the behavioural deficit observed in the Katz model; dopaminergic, GABA ergic, cholinergic agents and benzodiaeperies ere found to be ineffective.[23] Moreover, the possibility the adaptation of 5HT2 receptors following Asvagandha treatment is related to the antidepressant action in clinical situation is considerably strengthened by the fact that following ECS therapy (still considered as the most effective therapy), both 5HT2 receptor responsiveness, as well as 5HT2 receptor binding in cerebral cortex are significantly enhanced in animal models.[14,25,34]

In summary, 8 week Asvagandha-treated normal tats exhibited ore emotional stability in open field test compared to pre-drug level as well as control chronic Asvagandha treatment resulted in enhancement of 5HT2 receptor responsiveness and a reciprocal decrease in 5HT1A receptor responsiveness. Also, 8 week Asvagandha treatment (prophylactically) prevented the behavioural deficit in an animal model of depression. This was associated with an remarkable enhancement in the sensitivity of 5HT2 receptor responsiveness. The effect of Asvagandha on the 5HT receptor subtypes are similar to the action of several antidepressant drugs.

Acknowledgement

This work was supported partly by CSIR (New Deli) and by U.G.C The authors gratefully acknowledges Prof. P.K. Dey for their valuable guidance during the study and preparation of manuscript.

Table -1

Schedule of stressors administered (the schedule was repeated after 21 days)

Day	Type of Stressors	Duration
1	Restraint stress	5 min
2	Cold stress, 0oC	15 min
3	Shake stress	30 min
4	Individual housing	24hr
5	Individual housing	24hr
6	Food deprivation	24hr
7	Noise stress, 95 db	5 min
8	Cold water stress 0oC	5 min
9	Soiled cage	24hr
10	Reversal of day/night	24hr
11	Reversal of day/night	24hr
12	Food deprivation	24hr
13	Noise stress, 95 db	5 min
14	Cold water swin	5 min
15	Restraint stress	5 min
16	Tail pinch	5 min
17	Heat stress 380C	15 min
18	Food deprivation	24hr
19	Reversal of day/night	24hr

20	Noise stress, 95 db	5 min
21	Food deprivation	24hr

Table -2

Open field behaviour of rats during 4 week and 8 week Asvagandha administration (100mg/kg given orally)

Group	Ambulation	Rearing	Pellet
Control (n =10)			
0 week	87.2 ± 6.9	18.5 ± 2.7	2.6 ± 0.6
4 week	83.5 ± 5.2	16.2 ± 1.1	2.0 ± 0.8
8 week	89.5 ± 2.3	17.1 ± 0.9	2.0 ± 0.9
Control ± Asvagandha (n =10)			
0 week	86.3 ± 7.3	15.6 ± 0.9	2.6 ± 0.6
4 week	89.0 ± 7.2	21.2 ± 3.9	0
8 week	108.0 ± 8.7*	19.4 ± 2.5*	0*

Data expressed as Mean ± S.E. N= Number of animal used.
*P<0.005 compared to 0 week value of control + Asvagandha

Table -3

Open field behaviour of rats in depression group and depression + Asvagandha group.

Group	Ambulation	Rearing	Pellet
Control (n =10)	80.5 ± 10.7	18.4 ± 2.3	0
Depression (n=10)			
0 week	84.2 ± 9.08	17.0 ± 3.5	1.8 ± 0.8
4 week	59.1 ± 2.5 **	10.1 ± 1.3 **	4.7 ± 0.6*
8 week	36.0 ± 10.3***	2.5 ± 0.3***	2.4 ± 2.5
Control± Asvagandha (n =10)			
0 week	96.6 ± 7.3	20.2 ± 2.9	0
4 week	80.2 ± 6.6	15.4 ± 2.5	1.7 ± 0.73
8 week	95.7 ± 15.4 ***	16.2 ± 3.1***	1.2 ± 0.09

Data expressed as Mean ± S.E. N= Number of animals. Data analysed by 1 way ANOVA followed by students t- test *** P< 0.001 significantly different from prestress level (0 week). *** P< 0.001 compared to 8 week depression group.

Table -4

5HT1A receptor mediated 5HT syndrome elicited by 8-OH-DPAT (0.75 mg/kg, IP) in normal control, and after 4 week and 8 week Asvaganda treatment

Components of 5HT Syndrome	**Control**	**Control + 4 wk Asvagandha**	**Control + 8 wk Asvagandha**
Tremor	9.00 ± 0.6	10.1 ± 0.8	7.8 ± 0.66**
Flat posture	22.4 ± 2.2	15.3 ± 2.8*	11.0 ± 1.9**
Forepaw treading	3.3 ± 0.8	1.3 ± 0.9*	3.4 ± 1.5
Head weaving	12.4 ± 1.2	12.8 ± 1.7	18.2 ± 0.9**
Straub tail	2.2 ± 1.5	3.3 ± 0.9	2.4 ± 0.74
Hypothermia	-0.70 ± 0.2	1.8 ± 0.02	-1.2 ± 0.35

Data expressed as Mean ± S.E. N = Number of rats. Data analysed by Mann- Whitney U- test; P<0.05; **P<0.01 significantly different form control group.

Table -5

5HT syndrome elicited by 8-OH-DPAT (0.75 mg/kg, IP) in normal control, depression and depression + Asvagandha group.

Components of 5HT Syndrome	**Control**	**Depression (8 wk stress)**	**Depression + Asvagandha**
Tremor	9.00 ± 0.6	11.6 ± 0.8*	8.1 ± 0.5*
Flat posture	22.4 ± 2.2	16.4 ± 2.4**	12.4 ± 1.2*
Head weaving	12.4 ± 1.2	12.0 ± 0.9	13.2 ± 1.6
Straub tail	2.2 ± 1.5	3.0 ± 1.4	2.2 ± 0.1
Hypothermia	-0.70 ± 0.23	-1.96 ± 1.1	-2.3 ± 0.14*

Data expressed as Mean ± S.E. N = Number of rats. *P<0.05; **P<0.01 compared to control. *P< 0.05 compared to depression.

Table -6

5 MeO – DMT and Quipazine elected 'Wet dog shake' response (5HT2 receptor mediated) in control, 4 and 8 week Asvagandha treated, depression and depression + Asvaganda

Group	**Control (n=5)**	**Cont + 4 week asva. (n=5)**	**Cont + 8 week asva. (n=5)**	**Dep. (n=5)**	**Dep. + 4 week asva. (n=5)**	**Dep. + 8 week asva. (n=5)**
5MeO – DMT (5mg/kg)	5.2 ± 0.9	7.3 ± 0.5	9.3 ± 0.5*	4.5 ± 1.1	7.0 ± 1.1	13.1 ± 0.6**
Quipazine (1mg/kg)	15.0 ± 1.5	--	--	13.5 ± 0.6	18.8 ± 2.3	26.2 ± 1.5***

Data expressed as Mean ± S.E. N = Number of rats. *P< 0.05 compared to control **P<0.01; ***P<0.01 compared to depression group.

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