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Research Article

Influence of cyproheptadine on clomipramine induced sexual dysfunction in male rats

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ABSTRACT

Background: In our earlier studies we have reported that clomipramine (clmp) has the ability to suppress male rat sexual behaviour. It was also reported that clomipramine produced dose dependent and time dependent decrease in the testosterone levels and also damage to the testes.
Methods: In the present investigation we have challenged the male rats which were under treatment with clomipramine with cyproheptadine a serotonin antagonist. The treatment was continued for 60 days. At the end of 30 days half of the animals in each group were sacrificed blood was collected through cardiac puncture, serum was separated subjected for the estimation of serum testosterone and prolactin. At regular intervals all the male rats under treatment were challenged with female rats which are in oestrous stage and various sexual behaviour parameters were studied for 30 minutes under dim red light.
Results: The result reveals that prior treatment with cyproheptadine prevented the decline in testosterone levels induced by clmp, testicular damage was also prevented successfully with cyproheptadine at ½ TD and TD doses of clmp, but failed to maintain at higher doses. The sexual competence of male rats like mount latency, intromission latency, ejaculation latency and other sexual behaviour parameters also restored to normal in the ½ TD clmp treated group. In the rats treated with TD and 2TD clmp only partial improvement was observed.
Conclusions: The cyproheptadine a drug used as appetizer has the ability to elevate testosterone levels; it has also protected the testis from clomipramine induced damage. The sexual behaviour of the rats which were under treatment with clomipramine was also restored partially in TD and 2TD whereas the rats which were under ½ TD clmp treatment were restored to normal.

Keywords: Cyproheptadine 5HT2A antagonist, Clomipramine, Testosterone, Male rat sexual competence, TD, Testicular damage

INTRODUCTION

Psychic depression is a disorder that requires treatment for longer periods. It is known to be precipitated because of excessive metabolism of centrally located monoamines particularly serotonin. Hence monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA) and specific serotonin inhibitors (SSRI) are used for its treatment. The antidepressants elevate the monoamines particularly serotonin for its effect in the treatment of depression. In doing so they produce sexual dysfunction as rise in central serotonin leads to decreased libido. Clomipramine (Clmp) is the imipramine analogue of chlorpromazine. Due to its action against anxiety disorders and panic attacks, it is the only drug with 2 entries in the essential drugs list of the WHO. Regarding the compulsive disorders it is now the "gold standard" of therapy against which other drugs are measured.[1-4] In addition to SSRI action it has the ability to block cholinergic, adrenergic and dopaminergic receptors

which may contribute to its sexual dysfunction.[5] It was shown that 96% of males and females on clomipramine suffered from delayed orgasm representing the highest rate of antidepressant induced sexual dysfunction with any medication and it was consistent with clomipramine's potent serotonergic activity.[6]

The sexual function involves central, and peripheral neuronal activity, hormonal activity, and peripheral cellular activity. Compared to other tricylic antidepressants, it has greater effect on dopamine blockade and serotonin reuptake inhibition.[7] These implicate for prolactin release and orgasmic dysfunction mediated through 5-HT2 receptors.[8,9] Moreover peripheral antimuscarinic and alpha adrenergic blockade effects have been implicated in the clomipramine induced sexual dysfunction.[10-13] It was also reported in our studies that clmp dose dependently and time dependently decreased the testosterone levels, sexual competence of male rats and damaged the testes.[14] In another study amantadine failed to antagonize clomipramine induced sexual dysfunction in male rats.[15] Various treatment strategies exist for antidepressant induced sexual dysfunction. They are 1) try waiting (which does not really work) for spontaneous remission of symptoms as tolerance to the drug may develop, 2) decreasing the dose of the current antidepressant or 3) switching to a different antidepressant.[16] Although sometimes effective these strategies scare patients as switching to a different antidepressant that works in one may not work as well in another. The decrease in the dose of the current drug and/or taking a drug holiday (purposely skipping medication for a period of time when sexual activity is anticipated) may cause relapse of depression. The prevention of the relapse / worsening of depression are of utmost importance to the patient even more so than a healthy sex life. Therefore the most promising treatment is to stick to the current effective antidepressant and add another medication (or antidote) by a trial and error method to suppress sexual side effects. However no perfect solution exists to date as these antidotes have their own adverse effects and hence the search for proper medication be continued.

Cyproheptadine in a dose between 2-16 mg should be taken 1-2 hours before sexual activity as needed. If not cured, it should then be taken daily. The drug cyproheptadine (cypro) works as antihistamine with anti-serotonergic properties is often prescribed as an antidote for antidepressant induced sexual dysfunction. A dose between 2-16 mg should be taken 1-2 hours before sexual activity as needed. If not cured, it should then be taken daily.[16-18]

No information is available regarding its effectiveness as an antidote for clomipramine induced SD in males regarding its central and peripheral mechanisms associated with sexual activity. In fact such information can be obtained by conducting studies in animal model. Hence the present work was conducted employing rat as animal model.

Animal preparation

A total of 48 Male and 48 female Sprauge-dawley albino rats were purchased from central animal house NIMHANS, Bangalore. All animals were housed in a group of six males and six females separately in plexi glass cages (62 x 40 x 21) in an acclimatized colony room (25±0.50c) maintained on 12/12 hours light/dark cycle. The rats were 4 months old. They weighed around 300-400 gm each and while the females 250-350 gm each. They were fed on commercial pellet feed and water was available adlibitum. Prior approval was obtained from institutional ethical committee for conducting the studies.

METHODS

Clomipramine Hcl: Psychotropic India Ltd., Ghaziabad

Cyproheptadine: R.L fine chemicals, Bangalore

Carboxymethylcellulose (CMC): Nice chemicals, Cochin.

Diethyl ether: Nice chemicals, Cochin.

Eosin: Nice chemicals, Cochin

Estradiol benzoate: Sigma Aldrich, USA

Progesterone: Glen mark, Mumbai

Testosterone and prolactin kits: DPC, New York, USA

Haematoxylin: Nice chemicals, Cochin

Sesame oil: N. Ravindra Company, Mumbai

Rat feed: Sai Durga animal feeds, Bangalore

Animal treatment

The male rats were randomly divided into four groups of 12 male rats in each. Group I served as control, group II, III, and IV were treated daily with the therapeutic dose (TD) of cyproheptadine (1.8 mg/kg), 30 minutes later they were treated with (½ TD) clomipramine 13.5 mg/kg, clomipramine 27 mg/kg (TD) and 54 mg/kg of clomipramine (2TD) respectively for 60 days.[19,20] The maximum human therapeutic dose of clomipramine was extrapolated to rats based on the body surface area.[21] The control group received vehicle.

Male rat sexual behaviour was studied as explained elsewhere.[22]

Collection of blood sample and testes was half of the animals in each group on 30th day and remaining on 60th day were sacrificed for blood sample collection and histopathological examination of testes. Blood was collected through cardiac puncture using a 16 no needle under mild ether anaesthesia and was allowed to settle for some time. After centrifugation serum was separated and stored at- 20o for subsequent hormonal estimation. Testes were also collected and processed for the histopathological studies. Hormonal estimation and histology of the testes were studied.[23-25]

RESULTS

Table 1: Effect of chronic oral administration of cyproheptadine (cypro) and clomipramine (clmp) on sexual behaviour parameters of male rats.(data given as mean ±SEM).

Parameter Studied	Control				Cypro+clmp 13.5 mg/kg				Cypro+clmp 27 mg/kg				Cypro+clmp 54 mg/kg			
days	0	15	30	60	0	15	30	60	0	15	30	60	0	15	30	60
% mounted	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
% intromitted	100	100	100	100	100	100	100	100	100	75	75	50	100	50	50	50
% ejaculated	100	100	100	100	100	100	100	100	75	50	50	50	50	25	0	0
Mount latency	5.37 ± 0.84	8.5 ± 1.29	8.87 ± 1.02	7.5 ± 0.8	27.5 ± 5.26**	77.5 ± 2.5**	83.75 ± 1.8**	87.5 ± 2.5*	35.8 ± 2.4**	83.75 ± 4.19**	90 ± 5.9**	92.5 ± 4.72*	57.5 ± 3.1**	91.25 ± 4.4**	165 ± 16.7**	227.5 ± 22.86*
Intromission latency	23.5 ± 4.9	20.65 ± 4.8	18.62 ± 1.4	20.5 ± 1.8	125 ± 3.2**	157.5 ± 6.7**	155.5 ± 10.4**	128.71 ± 7.1*	170 ± 11.95**	586.25 ± 264.88**	601.5 ± 261.95**	992.5 ± 466.21*	188 ± 0.32**	1005 ± 301.44**	985.96 ± 308.28**	1395 ± 405.00*
Ejaculation latency	360 ± 18.4	375.5 ± 9.4	372.5 ± 8.8	375 ± 6.45	642.8 ± 95**	762.5 ± 74.1**	822.5 ± 80.1**	855 ± 130.4*	1312 ± 188.53**	1482.5 ± 1 57.23**	1305 ± 147.30**	1440 ± 207.86*	1317.5 ± 187.48**	1700 ± 90**	1800 ± 0**	1800 ± 0*
No of intromissions	15.6 ± 0.3	15.62 ± 0.3	15.37 ± 0.2	15.5 ± 0.2	17.625 ± 1.23	21.1 ± 0.6**	20.5 ± 1**	23.5 ± 0.8*	17.75 ± 3.4	10.75±3	13.125 ± 3.6	13.25 ± 7.6	14.00±2.8	5.25 ± 2.6*	4±1.6*	3.75 ± 2.2*
No of mounts	2.5 ± 0.32	2.25 ± 0.36	2.6 ± 20.4	3.5 ± 1.08	1.75 ± 0.16	3.125 ± 0.54	3.62 ± 0.26	4.75 ± 1.1	10±1.9**	10.75 ± 2.9**	10.62 ± 2.17**	9.5 ± 2.06*	9.1 ± 0.54**	7.87 ± 0.95	11 ± 1.19	5 ± 0.4
Post ejaculation Pause	262.5 ± 10.9	290 ± 30.9	225 ± 15.0	270 ± 19.14	380 ± 34**	452.5 ± 2.34**	397.5 ± 39.35**	365 ± 47.1*	1105 ± 263.1*	1300 ± 244.10**	1302.5 ± 242.91**	1150 ± 375.28	1122.5 ± 7.0644**	1635 ± 165**	1800 ± 0**	1800 ± 0*
Copulatory efficiency	0.85 ± 0.01	0.86 ± 0.2	0.85 ± 0.03	0.82 ± 0.04	0.88 ± 0.02	0.86 ± 0.02	0.84 ± 0.01	0.83 ± 0.02	0.58 ± 0.07**	0.51 ± 0.11**	0.54 ± 0.12*	0.4±0.23	0.55±0.06 **	0.23 ± 0.09**	0.18 ± 0.071**	0.28 ± 0.16*
Inter copulatory interval	23.1 ± 1.43	24.15 ± 0.5	24.29 ± 0.8	24.2 ± 0.7	45.3 ± 6.4**	36.23 ± 3.6**	41.8 ± 5.8**	36.97 ± 6.65	162.48 ± 71.06**	104.83 ± 26.11	82.5 ± 30.03	20.44 ± 11.84	170.5 ± 56.6**	115.8 ± 58.01	129.82 ± 57.04	125±75

Significant at P<0.05*, 0.01** compared to control (Mann Whitney 'U' test.

Influence of cyproheptadine on clomipramine induced decline in male rat sexual behaviour

Cyproheptadine increased the number of rats mounted, intermitted and ejaculated which were under treatment with clomipramine, when compared to their respective matching clmp treated controls. Cyproheptadine (cypro) in the dose tried (1.8 mg/kg) has successfully antagonized the sexual dysfunction induced by clmp13.5 mg/kg treatment. All the rats in this group exhibited mounting, intromission and ejaculation. Cyproheptadine prevented the decline in sexual competence in the male rats treated with clmp 13.5 mg/kg. In the group that received the therapeutic dose of clmp (27 mg/kg) cyproheptadine increased the number of intromissions and ejaculations when compared to its matching clmp treatment.

Suppression of mounting behaviour shown by the 2 TD clomipramine was well antagonized by cyproheptadine. All the rats in this group mounted on all the days studied. Cyproheptadine treatment reduced the ejaculation latency and post ejaculation pause when combined with clmp compared to their respective matching clmp treated controls, but failed to bring them back to normal. Copulatory efficiency and intercouplatory interval was better in cypro+clmp treated groups than clmp treated groups.

Cyproheptadine initially increased the intromission frequency in both TD and 2 TD doses of clomipramine. Gradually, increase in the mounting frequency followed by a decrease in the intromission frequency was observed indicating that cyproheptadine failed to maintain erection at higher doses of clmp. Cyproheptadine gradually decreased the mount latency and intromission latency when combined with clomipramine compared to their respective matching clomipramine alone treated groups. But failed to bring them back to normal during the period of study. Results were given in Table 1.

Influence of cyproheptadine on clomipramine induced changes in serum testosterone and prolactin levels in male rats

After 60 days of treatment no significant changes were observed in the control group and 13.5 mg clomipramine treatment group and also in 27 mg/kg clmp treatment. Cyproheptadine maintained the testosterone levels in the animals treated with 13.5 mg/kg and 27 mg/kg clomipramine. But failed to maintain the normal levels at 2 TD i.e. 54 mg/kg clomipramine treated group. Results

indicate that cyproheptadine TD successfully antagonized the clomipramine influence on the serum testosterone levels at ½ TD and TD levels of clomipramine whereas at 2 TD levels cyproheptadine has not offered any protection.

Table 2: Influence of cyproheptadine and clomipramine on serum testosterone and prolactin levels in male rats (data given as mean + SEM N=6).

Treatment	Testosterone ng/ml (30 days treatment)	Testosterone ng/ml (60 days treatment)
control	6.55±0.66	5.07±0.3
cypro+clmp 13.5 mg/kg	7.72±0.3	6.3±0.45
cypro+clomp 27 mg/kg	5.65±0.3	6±0.4
cypro+clmp 54 mg/kg	4.2±0.5*	2.7±0.2**

Cypro = cyproheptadine: clmp= clomipramine; Significant at P <0.05*, 0.01** compared to control (student "t" test)

Cyproheptadine and clomipramine treatment and its influence on testicular parameters

No significant changes were observed in the prolactin levels throughout the experiments. Results were given in Table 2.

No significant changes were observed in the cyproheptadine+clomipramine 13.5 mg/kg and cyproheptadine+clomipramine 27 mg/kg treated groups. The testicular parameter counts of spermatogonia, preleptotene, pachytene, secondary spermatocytes were maintained within the normal range. Hence it can be concluded that cyproheptadine offered good protection against the damage induced by ½ TD and TD doses of clomipramine but failed to protect the changes in testes produced by 2 TD clmp. At the end of 60 days also cyproheptadine offered better protection in the 13.5 mg and 27 mg/kg clomipramine treated groups. Results were given in Tables 3 and 4 and shown Figure 1 to 7. To SSRI action clomipramine has the ability to block adrenergic, cholinergic and dopaminergic receptors which also contribute for sexual dysfun.

Table 3: Cyproheptadine and clomipramine treatment (30 days) influence on histology of testes (data given as mean + SEM, N=6).

Treatment (30 days)	Sertoli cells	SP Gonia	Preleptotene	Pachytene	S. Spermatocytes
control 1 ml/kg	2.75±0.47	8±0.40	22.5±0.6	26.5±0.6	49.75±2.0
cypro+clmp 13.5 mg/kg	3±0.4082	6.25±0.25	22.75±0.8539	28±1.080	49.75±1.601
cypro+clmp 27 mg/kg	2.5±0.2	7.25±0.25	21.75±1.1	29.25±1.7	46.5±1.19
cypro+clmp 54 mg/kg	2.25±0.25*	5±0.4082**	15±1.082**	23.5±0.866*	40±0.913**

Cypro = cyproheptadine: clmp= clomipramine; Significant at P <0.05*, 0.01** compared to control (student "t" test)

Table 4: Cyproheptadine and clomipramine treatment (60 days) influence on histology of testes (data given as mean + SEM, N=6).

Treatment (30 days)	Sertoli cells	SP Gonia	Preleptotene	Pachytene	S. Spermatocytes
control 1ml/kg	3.5±0.288	8.25±0.4	21.25±0.8	27±0.4	48.75±0.75
cypro+clmp 13.5 mg/kg	2.75±0.25	7.5±0.2887	22.5±0.645	26.5±0.645	50±0.9129
cypro+clmp 27 mg/kg	2.25±0.25*	7.25±0.25	22.5±1.5	26±1.7	47.75±0.85
cypro+clmp 54 mg/kg	2±0.408	5.25±0.478**	15±0.913**	24.75±1.11*	41±0.846**

Significant at P <0.05*, 0.01** compared to control (student "t" test)

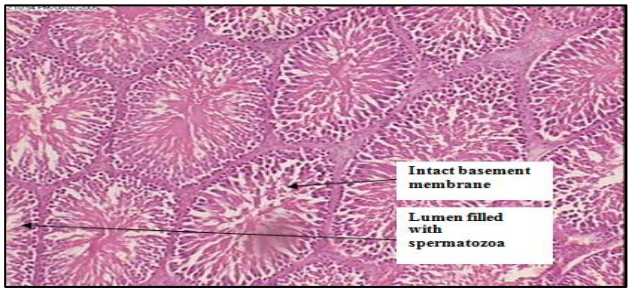

Figure 1: Cross section of seminiferous tubules. Cyproheptadine+clmp13.5 mg/kg 30 days treatment 400x.

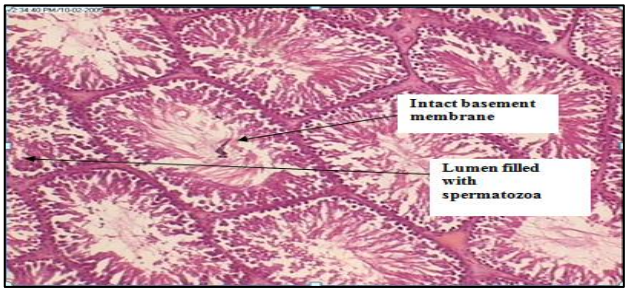

Figure 2: cross section of seminiferous. Tubulescyproheptadine+clmp 27 mg/kg 30 days treatment.

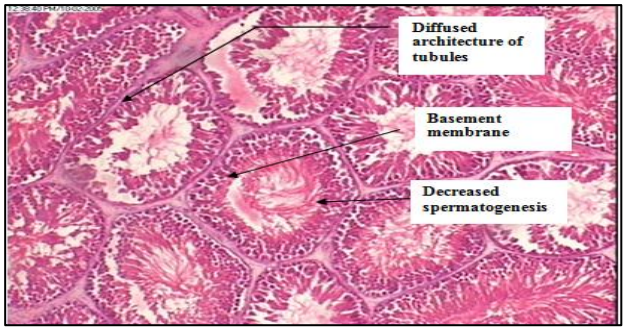

Figure 3: Cross section of seminiferous tubules. Cyproheptadine+clmp 54 mg/kg 30 days treatment 400x.

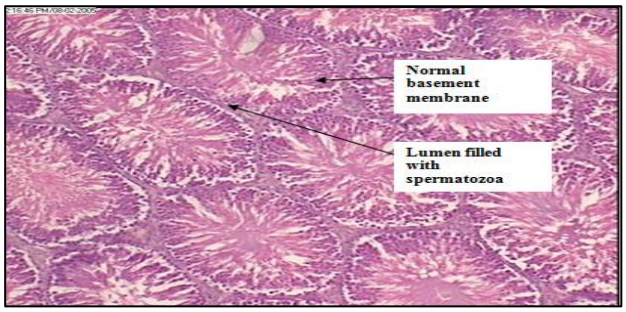

Figure 4: Cross section of seminiferous tubules. Cyproheptadine+clmp13.5 mg/kg 60 days treatment 400x.

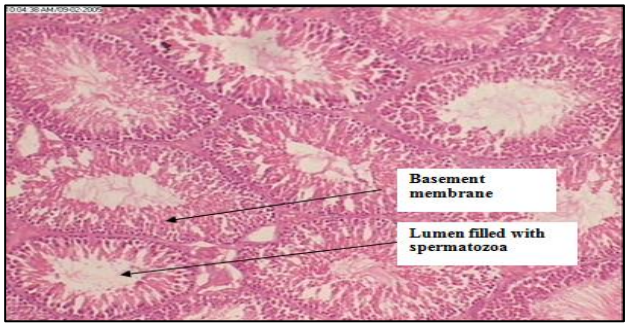

Figure 5: Cross section of seminiferous tubules. Cyproheptadine+clmp 27 mg/kg 60 days treatment 400x.

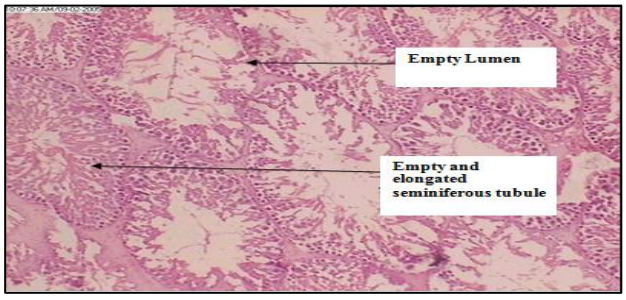

Figure 6: Cross section of seminiferous tubules. Cyproheptadine+clmp 54 mg/kg 60 days treatment 400x.

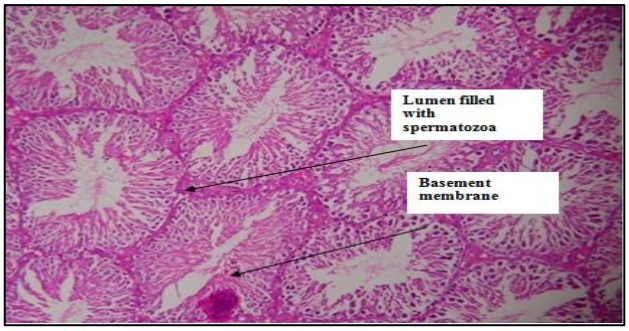

Figure 7: Cross section of seminiferous tubules. Control 400X (normal).

DISCUSSION

The improvement in central, hormonal and peripheral cellular effects with cyproheptadine could be due to its serotonin (5-HT2A) receptor blockade. The importance of this part of the work was that it revealed the peripheral benefits in addition to central effects. Our results are in agreement with the earlier findings.[26,27]

Serotonin acts at both central and peripheral receptors in the mediation of sexual function. Centrally, serotonin appears to down regulate and diminish the levels of mesolimbic dopaminergic activity and elevate prolactin, resulting in decreased libido.[28,29] Increase in prolactin level was not seen in our studies. In addition, serotonergic activation of different receptor sub-types has differential effects on sexual functioning. Studies in rats suggest that activation of receptor subtype 1A lowers the threshold for ejaculation. In addition, stimulation of 2C receptors appears to facilitate sexual behaviour in animal model. But activation of 2A, 1B or 1C inhibits sexual behaviour.[30] The above concept is summarized and given below.

A vast majority of the body's serotonin receptors are outside the brain and it may be that serotonin's peripheral activities are even more relevant to the sexual function than its central effects. Peripherally, at spinal or end organ receptors, serotonin has inhibitory effects on ejaculation in animals.[31,32] It may be due in part to serotonin's direct relaxing effects on vascular smooth muscle. Serotonin also acts on the smooth muscles of the genitals themselves, possibly inhibiting the muscular contraction that characterized orgasm. Further serotonin acts at peripheral nerves, where it appears to affect the flow of genital sensory information. Case reports have associated penile and vaginal anaesthesia with the use of serotonergic antidepressants.[33-36] Lastly, serotonin may delay orgasm through pre-synaptic inhibition of adrenergic transmission.[32]

While increased serotonin was found to associate with decreased sexual function, the decrease in serotonin level was not correlated with increased sexual function. The drug cyproheptadine is an antagonist of 5-HT 2A

receptors. Serotonin acts on several receptors namely 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7 37. The actions on 5-HT2A and other receptors except 5-HT1A and 5-HT2c leads to sexual dysfunction. The drug cyproheptadine being antagonist of 5-HT2A receptors antagonizes the serotonin reduced sexual function. Infact clomipramine produces sexual dysfunction by increasing the serotonin level due to its selective serotonin reuptake inhibiting activity. Hence cyproheptadine could antagonize the clomipramine induced sexual dysfunction at ½ TD dose of clomipramine with respect to central, hormonal and peripheral parameters. At TD of clomipramine cyproheptadine partially antagonized the central effects, and fully antagonized the hormonal and peripheral damage. However the damaging effect of 2 TD was partially antagonized. Usually clinical use of 2 TD of clomipramine does not arise. Hence cyproheptadine can be considered as a partial antagonist of clomipramine.

The literature revealed that the blockade of 5-HT2A receptors increased cortical dopamine release via 5-HT1A receptor stimulation indicating the involvement of dopamine also in the improvement of sexual function.[38]

In conclusion this study demonstrated that cyproheptadine successfully prevented the clomipramine induced decline in testosterone levels at ½ TD and TD clmp dose levels. But failed to antagonize the clomipramine influence at 2 TD levels. Even the testicular damage also prevented with the therapeutic dose of cyproheptadine in the animals treated with ½ TD and TD clmp treated groups. But failed to maintain at the 2 TD clmp dose levels.

The sexual competence of male rats also protected at the ½ Td clmp treated group. Where as in the TD and 2 TD clmp treated group only partial protection was observed.

CONCLUSION

To conclude cyproheptadine offered good protection against the clomipramine induced testicular damage which could be due to its ability to release FSH and testosterone hormones .The improvement in the sexual competence with cyproheptadine might be due to its ability to block 5 HT2A receptors leading to increase in the cortical dopamine level.

The study also indicated that it has no effect on the double the therapeutic dose of clomipramine induced sexual dysfunction.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Rothschild AJ. New directions in the treatment of antidepressant induced sexual dysfunction. Clin Ther. 2000;22:42-61.
2. Baldwin DS. Psychotropic drugs and sexual dysfunction. In Rev Psychiatry. 1995;7:262-73.
3. Lane FM. A critical review of SSRI related sexual dysfunction including possible etiology and implications for management. J Psychopharmacol. 1997;11:72-82.
4. Fava M, Ramkin M. Sexual dysfunction and SSRIs. J Clin Psychiatry. 2002;63:13-6.
5. Bernick M, Vieira AHG, Nunes PV. Bethanechol chloride for treatment of clomipramine induced orgasmic dysfunction in males. Rev Hosp Clinic Fac Med Paulo. 2004;59(6):357-60.
6. Monteiro WO, Norshirvani HF, Marks IM. Anorgasmia from clomipramine in obsessive-compulsive disorder: a controlled trial. Br J Psychiatry. 1987;151:107-12.
7. Blackwell B. Antidepressant drugs. In: Dukes MN Meyer's side effects of drugs. Elsevier, Amsterdam; 1984:24-61.
8. Jones RD, Lacombe DK, Groom GV. Plasma prolactin concentration in normal subjects and depressive patients following oral clomipramine. Post grad med Journal. 1977;53:166.
9. Pomerantz SM, Hepner BC, Wertz JM. Serotonergic influence on male sexual behavior of rhesus monkeys effects of serotonin agonists. Psychopharmacology (Berl). 1993;111:47-54.
10. Sorscher SM, Dilsaver SC. Antidepressant induced sexual dysfunction in men due to cholinergic blockade. J Clin Psychopharmacology. 1986;6:53.
11. Beaumont G, Mayes A. Do task and sex differences influence the visual evoked potential? Psychopharmacology. 1977;14:545-50.
12. Aizenberg D, Zemishlany Z, Hermesh H, Karp L, Weizman A. Painful ejaculation asssociated with antidepressants in four patients. J Clin Psychiatry. 1991;52:11:461-3.
13. Balon R, Yeragani VK, Pohl R. Sexual dysfunction during antidepressant treatment. J clin psychiatry. 1993;54:209-12.
14. Devang SS, Satyanarayana S, Kumar E, Vivek B. Clomipramine affects sexual behavior and reproductive functions in male rats. International Journal of Health Sciences. 2010;3(3):341-7.
15. Devang SS. Satyanarayana SK, Kumar E, Kumar A. Amantadine failed to antagonize the clomipramine induced sexual dysfunction in male rats, Oman Medical Journal. 2011;26(6):404-9.
16. Gitlin MJ. Effects of depression and antidepressants on sexual functioning. Bulletin of the Menninzer Clinic. 1995;59(22):232-48.
17. Sovner R. Treatment of Tricyclic antidepressant induced orgasmic inhibition with cyproheptadine. J Clin Psychopharmacology. 1984;4:169.

18. Riley AJ, Riley EJ. Cyproheptadine and antidepressant induced anorgasmia. Br J Psychiatry. 1986;148:217-8.
19. Marks IM, Stern RS, Mawson D. Clomipramine and exposure for obsessive-compulsive rituals. I Br J Psychiatry. 1980;136:1-25.
20. Ananth J, Pecinold JC, Vandensteen N. Double blind comparative study of clomipramine and amitriptyline in obsessive neurosis. Prog Neuro Psychopharmacology. 1981;5:257-62.
21. Paget GE, Barner JM. Evaluation of drug activities, pharmacometrics ed. Laurence and Bacharach. Academic press, New York. 1964;1.
22. Ratnasooriya WD, Jayakody JRAC, Dharmasiri MG. Sodium nitroprusside impairs the sexual competence of male rats Human and experimental toxicology. 2004;23:4187-92.
23. Culling CFA, Rath MRC. Cellular pathology technique. Butter worth publisher. FIMLS Vancover Canada. London. 1976;4:29-138.
24. Verma PK, Sharma A, Mathur A, Sharma P, Gupta SC, Dixit VP. Effect of sarcostemma acidum stem extract on spermatogenesis in male albino rats. Asian J of Andrology. 2002;4(1):43-7.
25. Abercrombie M. The anatomical record. 1946;94:239-47.
26. Sarkar SL, Roy DK, Jogi KV. Effect of cyproheptadihydrochloride on spermatogenesis. experentia. 1975;31(11):1367-8.
27. Quing H, Bai K, Gao ER. Effects of cyproheptadine on hypothalamus-pituitary-gonad axis and calmodulin gene expression in rats. Chinese journal of pharmacology and toxicology. 2003;17(3):161-6.
28. Rosen RC, Lane RM, Menza M. Effects of SSRI s on sexual functions, a critical review. J Clin Psychopharmacol. 1999;19:67-85.
29. Zajecka J. Strategies for the treatment of antidepressant related sexual dysfunction. J clin psychiatry. 2001;62(suppl 13):35-43.
30. Bitran D, Hull EM. Pharmacological analysis of male rat sexual behavior. Neuro Sci Biobehav Rev. 1987;11:365-89.
31. Meston CM, Frohlich PF. The neurobiology of sexual function. Arch Gen Psychiatry. 2000;57:1012-30.
32. Zajecka J, Fawcett J, Schaff M, Jeffriess H, Guy C. The role of serotonin in sexual dysfunction, fluoxetine-associated orgasm dysfunction. J Clin Psychiatry. 1991;52:66-8.
33. Neill JR. Penile anesthesia associated with fluoxetine use. Am J psychiatry. 1991;148(11):1603.
34. King VL, Horovitz IR. Vaginal anesthesia associated with fluoxetine use (letter). Am J Psychiatry. 1993;150:984-5.
35. Gitlin MJ. Psychotropic medications and their effects on sexual function, diagnosis, biology and treatment approaches. J Clin Psychiatry. 1994;55(9):406-13.
36. Ellison JM. Antidepressant induced sexual dysfunction a review classification and suggestions for treatment. Harvard Rev Psych. 1998;6:177-89.
37. Goodman and Gilman's. The pharmacological basis of therapeutics. McGraw Hill, Medical publishing division; 2001:10:269-90.
38. Icihikawa J, Ishii H, Bonaccrso S, Wiley L, Fowler AO, Laughlin I, et al. 5-HT2A and D2 receptor blockade increases cortical DA release via 5- HT1A receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. Journal of Neuro Chem. 2001;76:1521-31.

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