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NEUROTRANSMITTER, OPIODERGIC SYSTEM, STEROID–HORMONE INTERACTION AND INVOLVEMENT IN THE REPLACEMENT THERAPY OF SEXUAL DISORDERS

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Summary—Dopamine (DA) and serotonin (5-HT) are the neurotransmitters most directly involved in sexual activity. DA plays a stimulatory role while 5-HT has an inhibitory effect. The two monoaminergic systems modulate the secretion of many hormones (GnRH, LH, testosterone, prolactin and endorphins) involved in sexual functional capacity. Furthermore, hormones influence synthesis and storage of brain neurotransmitters. Impotence can often be associated to clinical depression and altered neurotransmitter function. Moreover, stress represents an unbalance between various neurotransmitter systems and can induce impotence especially when disorders of the endorphinic system are present. Replacement therapy is based upon the understanding of these basic concepts. Impotence due to an underlying depressive illness must be treated with dopaminergic antidepressant drugs; while in stressful conditions a good response to the naloxone test is the preliminary criterion to subsequent naltrexone treatment. When a hormonal deficiency has been proved, the hormone replacement therapy is of course highly effective (gonadotropins in hypogonadotropic syndromes, testosterone in aging, etc.). Finally, idiopathic impotence could be treated by DA agonist and/or 5-HT antagonist drugs either alone or better yet in association with psychotherapy.

INTRODUCTION

Normal male sexual function depends on complex interactions between the environment and the nervous, vascular and endocrine systems of an individual.

A pure hormonal disturbance is considered a rare primary cause of impotence; vascular and neurological disorders also represent only a small percentage of the whole problem.

The great majority of clinical cases of impotence deals with so-called "psychological problems" [1], that is the interaction between the human mind and the environment.

Sexuality therefore originates in the brain. The complex network of neurotransmitters and neuromodulators are in a delicate equilibrium that can be disrupted in response to environmental stimuli bringing about impotence in predisposed individuals. Serotonin and dopamine are the two neurotransmitters mostly involved in sexual behavior while among the neuromodulators the endorphinic system appears to have a primary role.

Androgen hormones have a fundamental role, not only in the imprinting process but also in toning up neurotransmission as will be discussed later on in the paper.

SEROTONINERGIC SYSTEM

The inhibitory effect of serotonin (5-HT) in sexual activity in animals either utilising 5-HT inhibitors [2–4, 8–10] and tryptophan free-diets [5], or 5-HT agonists [6, 7] has been repeatedly documented in literature.

Whenever we deal with humans, however, the situation is totally different. In fact, pharmacological attempts to modify central serotoninergic activity in humans does not induce significant or, in any case, repeatable modification of sexual behavior. In a study carried out by Sicnteri *et al.* on their patients who suffered from migraine as well as loss of libido, a combined treatment of pCPA and testosterone (T) significantly increased occurrence of nocturnal erection [11]. On the contrary, in a double blind study in which 10 patients were administered 1 g per day of pCPA per os for 4 weeks, there were

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no detectable therapeutic effects when compared to the data obtained in the placebo group [12]. The action of various antiserotoninergic substances, such as methisergide and metergoline, administered either alone or in association with mesterolone and bromocriptine to patients suffering from non-organic sexual impotence, has also been evaluated. None of the drugs produced clearly positive results [13].

DOPAMINERGIC SYSTEM

The dopaminergic system (DA) is diffused in the CNS as well as in various peripheral areas, such as the pelvis, the vas deferens, the penis. The stimulatory role that DA plays in male sexual behavior is well known and has been well documented by studies carried out on animals as well as on humans. DA agents increase the number of rats that mate with receptive females. This effect is completely blocked by the administration of dopaminergic receptor blocking agents such as haloperidol and pimozide [14, 15]. Inasmuch as L-DOPA, administered along with a peripheral inhibitor of dopadecarboxylase, not only augments the cerebral concentration of DA, but also decreases the cerebral concentration of 5-HT, the stimulatory effect on sexual behavior could be attributed to both mechanisms.

Data confirming the stimulatory effect of DA on human sexual behavior have also been reported. Evidence of an increase in sexual activity is noted when patients undergoing therapy for Parkinson's disease are administered L-DOPA or those being treated for acromegaly are administered bromocriptine (a powerful dopaminergic drug) [16, 17]. The sexual benefit shown by Parkinson patients after administration of L-DOPA is well evident even before improvement of the neurological symptoms. The same occurs in acromegalic patients in whom bromocriptine seems to improve sexual drive before or, in any case, independently from normalization of GH levels (even in cases with normal PRL values). In patients with PRL-secreting adenoma, the administration of bromocriptine brings the Vis Libido Rating Scale (VLRS) to normal values even before lowering plasma PRL levels [18] (Fig. 1). Positive and immediate effect on erection in normal men obtained with an infusion of piribedil, another DA agonist drug, has also been recorded [19]. Such prompt effect may be the result of a direct stimulation not only of the central but also of peripheral dopaminergic receptors and, in any case, cannot be explained on the basis of hormonal mechanism.

Recently researchers have been trying to shed greater light on the role that the dopaminergic system plays in impotence associated with hyperprolactinaemia as well as in ejaculation pathophysiology. It has been observed that administration of bromocriptine in impotent and hyperprolactinaemic patients determines a normalization of PRL levels as well as an increase in libido and an improvement of potentia coeundi. These hormonal and clinical results

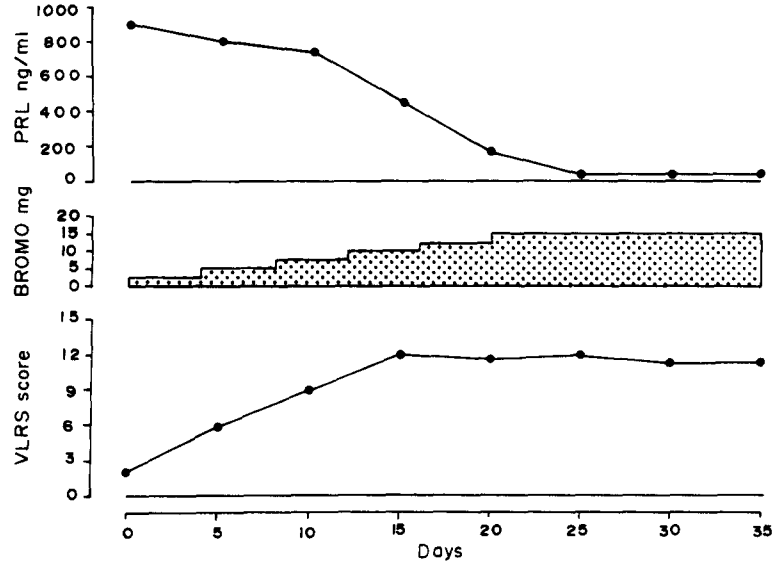

Fig. 1. Behavior of prolactin (PRL) and vis and libido rating scale (VLRS) score during bromocriptine treatment in a patient with PRL secreting pituitary adenoma.

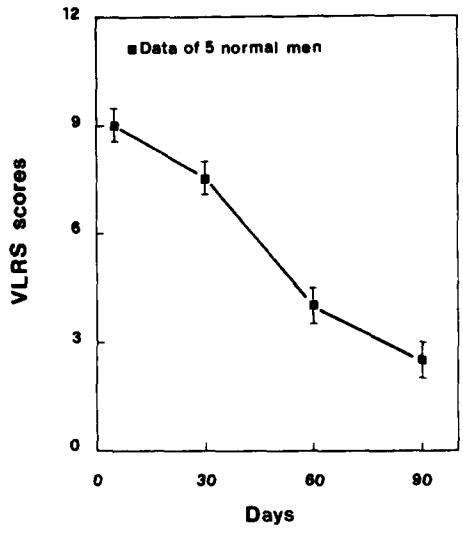

Fig. 2. VLRS during metoclopramide administration.

disappear with suspension of drug administration [18]. The pathogenic mechanisms underlying hyperprolactinaemic impotence and those through which bromocriptine induces positive therapeutic effects are still not fully understood: (1) Does hyperprolactinaemia have a direct inhibitory effect on the hypothalamus? and/or (2) Does low cerebral dopaminergic tone produce hyperprolactinaemia and impotence? In man the administration of metoclopramide (a dopaminergic receptor blocking agent which does go through the blood–brain barrier) induces loss of libido and the disappearance of spontaneous erection [20] (Fig. 2). Psychotic patients who undergo long-term treatment with dopaminergic blocking drugs (haloperidol, chlorpromazine, flufenazine) have a reduced sexual activity, while plasma PRL, LH and T values are normal [21]. The results obtained with the suspension of psychoactive drug treatment or with the administration of placebo or benzodiazepine indicate a trend towards recovery of sexual functions, that is, restoration of libido and spontaneous erection [18]. Thus, the hypothesis that dopaminergic blocking agents act at the cerebral level influencing sexual behavior regardless of modifications in PRL plasma levels seems to be highly possible.

Of related interest are the studies carried out on the relationship between the dopaminergic system and ejaculation. A double blind crossover study carried out with metoclopramide and placebo on a group of patients suffering from premature ejaculation demonstrated that metoclopramide, administered at a dosage which does not completely suppress sexual stimuli (10 mg twice per day, orally), significantly delays ejaculation [22] (Fig. 3). Bromocriptine administered orally (5 mg/day) to normal young volunteers induces premature ejaculation, whereas it seems to be of some help in shortening the delay of ejaculation in the aged [23] (Fig. 4).

Lisuride, a semi-synthetic ergot derivative, seems to have potential premises for fruitful treatment of male sexual disorders owing to its double mechanism of both dopaminergic and antiserotoninergic action [24–30]. With this drug we carried out a clinical double-blind crossover study on a group of 44 patients suffering of idiopathic impotence. The subjects were selected on the basis of our routine evaluation of male sexual disorders including clinical examination and history (CE), standard blood analyses (SBA), penile echodoppler (PD), neurological investigation using the sacral latency test (SLT), nocturnal penile tumescence test (NPT), plasma T profile determination (TP), GnRH test for LH and FSH, TRH test for PRL, psychological and psychometric evaluation through MMPI. The results were scored (0–2) on a sex adequacy scale (SAS) which evaluates sexual desire, frequency of

		Placebo			Metoclopramide		
	BAS	30	60	90	30	60	90
PRL (ng/ml)	8.3 ± 0.7	5.3 ± 0.4	6.0 ± 0.4	9.8 ± 0.5	38.9 ± 2.3•	14.7 ± 1.4*	9.0 ± 0.4
T (ng%)	653 ± 33	582 ± 27	670 ± 35	626 ± 35	719 ± 38	610 ± 22	538 ± 25
FSH (mUI/ml)	4.5 ± 1.7	6.7 ± 2.1	5.8 ± 0.9	5.9 ± 1.1	4.6 ± 1.3	5.3 ± 1.0	5.0 ± 1.1
LH (mUI/ml)	7.5 ± 2.0	7.0 ± 2.0	8.1 ± 1.7	6.4 ± 1.3	8.0 ± 2.2	6.6 ± 1.5	6.8 ± 1.6
VLRS	1.8 ± 0.2	2.2 ± 0.2	1.9 ± 0.2	1.5 ± 0.1	2.5 ± 0.3	2.7 ± 0.2°	2.9 ± 0.2•

° p<0.02; * p<0.01; • p<0.001

Fig. 3. Hormonal (mean ± SE) and VLRS (mean ± SE) evaluations in basal conditions (means of two different evaluations), during placebo and metoclopramide treatment in 10 men complaining of premature ejaculation.

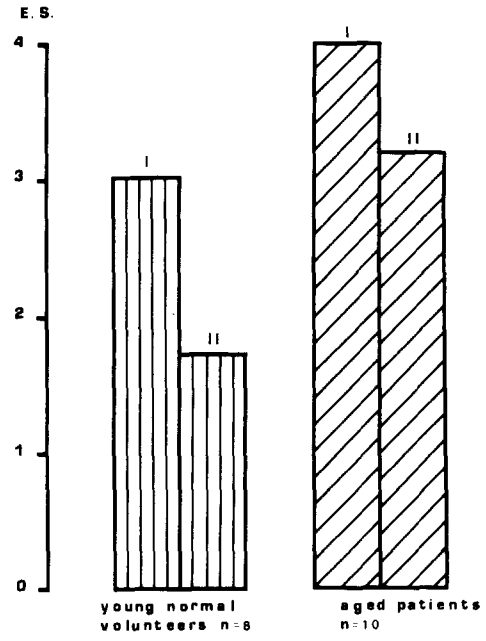

Fig. 4. Effect on ejaculation scale (E.S.) after bromocriptine administration (5 mg/day). Ejaculation scale (E.S.): 1. Premature ejaculation (before penetration); 2. premature ejaculation (after penetration); 3. normal ejaculation; 4. delayed ejaculation. I = Before treatment. II = After treatment.

masturbation, frequency and quality of sexual intercourse, ejaculation latency, climax intensity (Fig. 5). The overall results seem to show some positive effect on various parameters such as a major frequency of morning erection (++), and a major frequency of masturbation (+). As far as an eventual effect on sexual intercourse itself, we may only say that a slight improvement was observed with regard to frequency and to the presence of spontaneous, non-manipulated erection. Notable was the effect on ejaculation: nearly all the patients referred to a tendency towards premature ejaculation. The last observation could lead to a promising therapeutic efficacy of Lisuride in the aged where the problem of delayed ejaculation is well known.

ANDROGENS

The significance of androgens in sexual behavior is widely known. Well known is the fundamental role played by T (at the beginning of the second trimester of intrauterine life) in determining sexual differentiation, first in the brain and then in the periphery [31, 32]. Also well known is the "priming effect" exerted by T on the CNS during pubertal stages [33]. A relatively more recent finding is the ability of T to positively interfere with central neurotransmission. In fact, some evidence indicates that T acts on the brain through the activation of the dopaminergic system and the inhibition of the serotoninergic system. Castration of adult male rats causes a decline in cerebral levels of DA while at the same time an increase in cerebral 5-HT occurs; exogenously administered, T reverses the castration-induced reduction in cerebral DA content [34, 35]. On the other hand, normal plasma T levels are found in numerous men who are impotent, whereas T levels below the normal range are at time observed in men who are sexually active [23]. Furthermore, the administration of high doses of T in impotent men, regardless of their own plasma levels of T,

Sex adequacy scale (arbitrary scale 0–2)	P = Placebo L = Lisuride	I → II P(n = 21)	I → II L(n = 12)	I → II L(n = 23)	I → II P(n = 16)
Total score	17 ± 7.6	19 ± 5.9	29 ± 8.1	25 ± 8.6	17 ± 6.2
(1) Sexual desire	5 ± 2.5	5 ± 1.8	8 ± 2.0	7 ± 2.5	5 ± 2.1
Sexual fantasies	1 ± 0.6	1 ± 0.5	1 ± 0.9	1 ± 0.6	1 ± 0.4
Morning erections	1 ± 0.6	1 ± 0.8	2 ± 0.5	1 ± 0.7	1 ± 0.6
Sexual approach	1 ± 0.7	1 ± 0.4	1 ± 0.4	1 ± 0.4	1 ± 0.5
(2) Masturbation	1 ± 0.6	1 ± 0.8	1 ± 0.4	1 ± 0.7	0 ± 0.5
(3) Sexual intercourse	6 ± 3.5	7 ± 2.9	10 ± 3.5	9 ± 3.3	7 ± 2.7
Frequency	1 ± 0.6	1 ± 0.6	2 ± 0.5	1 ± 0.5	1 ± 0.3
Spontaneous erections	2 ± 1.1	2 ± 0.8	3 ± 1.0	2 ± 0.9	1 ± 0.7
Grade of erections	1 ± 0.7	1 ± 0.8	1 ± 0.5	1 ± 0.7	1 ± 0.5
(4) Ejaculation	3 ± 0.7	3 ± 1.8	5 ± 1.1	4 ± 1.7	3 ± 1.8
(5) Climax intensity	3 ± 1.6	3 ± 1.5	5 ± 1.3	4 ± 1.4	3 ± 0.8

Fig. 5. Double blind crossover study. Effect of lisuride hydrogen maleate (400 μg per os/day) in 44 impotent men (age = 41.3 ± 12.4 yr).

is totally useless [36]. Thus the role of T in the maintenance of the sexual behavior seems to be controversial: on one hand it seems sufficiently documented in its role in the central transmission of sexual stimuli, while on the other it seems irrelevant in clinical endocrinology. So once again it clearly appears that plasma T variations cannot be considered *per se* responsible for male impotence of psychogenic origin. It may be hypothesized that cerebral neurotransmitters and their interactions are fundamental in the physiological dynamics of sexual activity and that their unbalance due to psychological factors can determine either impaired peripheral plasma T levels or disregulation in behavioral sensitivity to T variations.

In order to verify the relevance of both psychological and endocrinological parameters in impotence, we carried out a study on a group of 52 patients complaining of sexual disorders of non-organic origin. This diagnosis was made by means of our routine evaluation of male sexual disorders (CE, SBA, PD, SLT, NPT). All the patients (aged between 27 and 61) were unable to initiate or, in any case, successfully complete sexual intercourse. They underwent endocrine and psychological studies. Endocrine study included RIA evaluation of plasma FSH and LH in basal condition and after GnRH stimulation (100 μg), plasma T profile and plasma PRL values in basal condition and after TRH stimulation (200 μg). Psychological study was carried out using psychometric tests for evaluation of personality, state of anxiety, depression, dynamics of sexual performance. A Sex Adequacy Scale Questionnaire (SAS) was utilized and the results were scored on an arbitrary scale. The analysis of SAS and APS (Anxiety and Pleasure Survey Schedules) [37] allowed a more precise and adequate definition of the sexual disorders in our patients. Fourteen subjects had had a total absence of erection due to a lack of libido for a period of time that varied between 6 months and 4 yr at the time of examination. The remaining 38 cases had difficulty with sexual behavior in that morning erection was inconstant and periods of more or less good sexual performance alternated with periods of more or less total sexual deficiency. Analysis of personality (evaluated through the Minnesota Multiphasic Personality Inventory—MMPI) [38] showed a group of 14 individuals who presented values typical of a depressive state. These patients were found to be the same whose responses to the SAS indicated a complete loss of libido and who had had an adequate sexual drive until a stressful event. On the contrary, the remaining subjects had just about always had sexual difficulties during their whole lives. This situation was successively confirmed and clarified by using the subscales for depression [39–42] and for masculinity–femininity [40–43] trends of MMPI. The ACL (Adjective Check List) [44] again showed a group of 14 depressed subjects against a group of 38 non-depressed patients. Impotence was the only common symptom of the two groups.

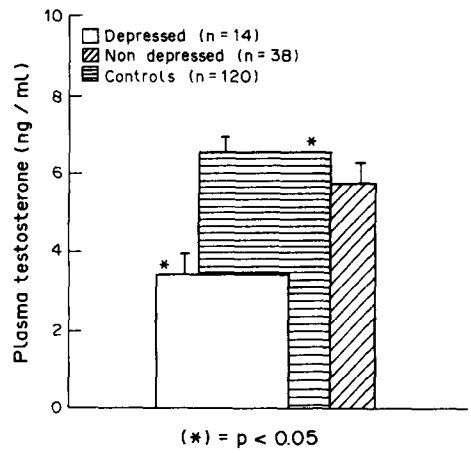

Fig. 6. Plasma testosterone levels in impotent men.

As far as endocrine investigation is concerned, plasma FSH and LH in basal condition and after GnRH as well as PRL levels in basal condition after TRH showed no significant difference between the two groups nor between the two groups and the controls. As far as T is concerned, the results showed a significant difference between the two groups and between the depressed patients and the controls (Fig. 6).

On the basis of these findings, the patients having low levels of T were treated with T-enantate: no significant positive effects were obtained. These subjects, along with those with normal levels of T, were successively treated with various dopaminergic drugs administered either alone or in various combinations (Fig. 7): aside from an evident positive effect on ejaculation, very often premature, positive results did not exceed 8%. Such poor results testify to the complexity of sexual problems and the gap still existing between basic and clinical information. We can only hypothesize that sex arousal disorders are very often correlated to particular personality traits. Stress can often disrupt a fragile equilibrium and can lead to hormonal modifications, of which lowered plasma T, more

	T		Br		BP		L		T+Br		T+L	
	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND
1 Sexual desire	+/−		−	−	−	−	−/+	+/−	+/−	−	−	+/−
2 Frequency of masturbation	−		−	+/−	−	−	−	+	−	−	−	−/+
3 Frequency of intercourse	−		−/+	+/−	−	−	−	+	+/−	+/−	+/−	+
4 Spontaneous erections	−		+/−	+	+	+/−	+	+	−/+	+	+/−	+/+
5 Grade of erection	−		−	−	−	−	−	−	−	−	−	−
6 Duration of erection	−		−	+/−	−	−	+	+/−	−	+/−	−	+
7 Ejaculation	−											
a − Premature			−	+/+	−	−	+/−	+/+	−	+	+/−	+
b − Regular			−	−	−	−	−	+	−	−	−	+/+
c − Delayed			−	−	−	−	−	−	−	−	−	−
8 Climax intensity	−		−	−	−	−	−	+/−	−	−	−	+/−

T = Testosterone enantate − 250mg i.m. every 15 days
Br = Bromocriptine − 5mg per os/day
BP = Brain Phospholipids − 100mg i.m./day
L = Lisuride − 400μg per os/day
D = Depressed patients − n = 14
ND = Non depressed patients − n = 38

Fig. 7. Open clinical trial on impotent men ($n = 52$, age = 27–61 yr).

than a cause of sex inadequacy, should be interpreted as a workable marker.

ENDORPHINIC SYSTEM

Closely related to stress and to catecholamines is the endorphinic system [45–52]. Furthermore, opioids are known to be involved in the modulation of sexual behavior in experimental animals as well as in humans. In rats, morphine and beta-endorphin inhibit male sexual ability [53]; in humans, exogenous opioids may determine a reduction in sexual arousal and erectile function [54]. On the other hand, treatment with opioid antagonists, naloxone (NAL) and naltrexone (NTX) can induce copulatory behavior in sexually inactive rats and facilitate sexual receptivity in female animals [55–57].

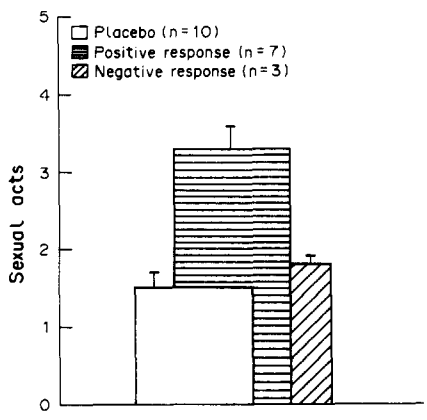

Fig. 8. Effect of naltrexone 50 mg/die for 2 weeks.

We tested whether treatment with NTX could be of therapeutic value in male impotence. Twenty patients, age ranging between 27 and 55 yr, with a stable-couple menage, with non-organic impotence lasting for at least one year and psychologically identified as "stressed" subjects according to psychometric survey (LES) [58] and MMPI, were studied. Patients were randomly divided into 2 groups of 10 patients each. One group was administered NTX per os (Trexan, DuPont) at a dosage of 50 mg/die (25 mg b.i.d.) while the other received placebo (PL) for two weeks. Sexual activity was assessed and scored on an arbitrary sexual acts evaluation scale (SAES) (Fig. 8). The results of the investigation showed that 7 patients out of 10 benefited from the short-term opioid antagonist treatment. In order to clarify the mechanism of action of this drug in male impotence, all the patients who had been administered NTX later underwent penile doppler evaluation before and after NAL i.v. injection (2 mg). Again, the same 7 patients who had responded positively to NTX showed an increase of penile blood flow within 30–45 min, while in the 3 remaining subjects there was no modification. It is interesting to note that in a separate experiment the injection of NAL into the corpora carvenous did not bring about any evident positive effect. On the basis of these preliminary observations, we can only hypothesize that in some kinds of impotence an increase in central opioidergic tone, most likely stress linked, could exist and be

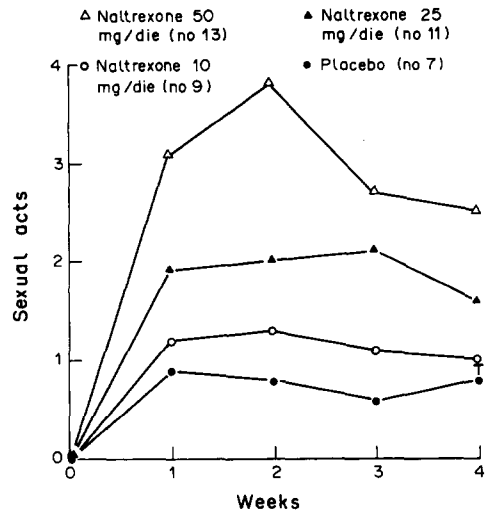

Fig. 9. Sexual activity during naltrexone administration at different doses (50, 25 and 10 mg) versus placebo.

involved in the down-regulation of sexual behavior.

While NTX seems to be sufficiently safe and to give positive results in a 2 week treatment of male sexual impotence, it does not seem to be appropriate in long-term administration due to its toxicity. Our present effort aims at finding the highest therapeutically effective dose in the longest period of time with the lowest toxic risk in a more clearly identified category of patients. Within this aim in mind, 33 non-organic impotent patients, identified as "stressed" subjects according to psychological and psychometric tests, were administered NTX for 4 weeks at different doses as follows: 50 mg/die ($n = 13$), 25 mg/die ($n = 11$), 10 mg/die ($n = 9$). The results of the study plotted against placebo ($n = 7$) were evaluated weekly and scored on an arbitrary sexual acts evaluation scale (SAES) (Fig. 9). The best findings were recorded with NTX at 50 mg/die at the end of the second week of treatment: in this group the scale score decreased at the end of the third week and dropped again at the end of the fourth. The patients who had been administered NTX at 25 mg/die showed a progressive improvement in their sexual activity

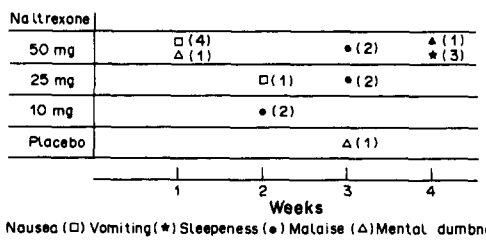

Fig. 10. Side effects during 4 weeks of naltrexone administration at different doses (50, 25 and 10 mg).

up until the third week of treatment; a decline in the scale score was registered towards the end of the fourth week. The administration of 10 mg/die of NTX brought about a slight improvement in sexual activity which, furthermore, remained constant during the whole observation period.

In some patients side effects consisting of nausea, malaise, sleepiness, mental dumbness, vomiting (Fig. 10) were recorded. They were more apparent in the 50 mg NTX dose group followed by the 25 mg group. No significant effects were reported in the 10 mg group or in the placebo group. The reduction in sexual activity observed at the end of the third week of treatment, more evident in the 50 mg group and less in the 25 mg group, seems to be determined by the toxic effect of the drug, since the decline of the former coincides with the appearance of the latter.

The data so far collected seem to indicate that opioid antagonists represent a new interesting and promising treatment in a well-defined category of patients. They appear to be very effective in the short-term treatment of subjects with high levels of stress. The administration of NTX, regardless of the dose (50–10 mg), 1–2 h prior to sexual approach does not exert any positive effect when compared to placebo, and long-term administration is greatly limited by the appearance of toxic effects. Therefore a new less toxic but therapeutically effective compound should be found.

In conclusion, numerous data indicate the possibility of treating male sexual disorders with pharmacological agents, many of which interfere with the dopaminergic and serotoninergic systems. Yet in humans the psyche has a strong influence on sexual behavior and pharmacological treatment alone still today does not always resolve the individual problem. A combination of psychotherapy, behavioral therapy and pharmacotherapy may provide the best treatment for impotent patients. Since each patient is unique, treatment programs must be tailored to the individual.

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REFERENCES

1. Money J. and Higham E.: Sexual behavior and endocrinology (normal and abnormal). In *Endocrinology* (Edited by L. J. De Groot). Grune & Stratton, New York, Vol. 3 (1979) p. 1353.
2. Tagliamonte A., Tagliamonte P., Gessa G. L. and Brodie B. B.: Compulsive sexual activity induced by

P-chlorophenylalanine in normal and pinealectomized male rats. *Science* **166** (1969) 1433–1435.
3. Malmnas C. O. and Meyerson B. J.: P-chlorophenylalanine and copulatory behavior in the male rat. *Nature* **232** (1971) 398–400.
4. Whalen R. E. and Luttge W. G.: P-chlorophenylalanine methyl ester: an aphrodisiac? *Science* **169** (1970) 1000–1001.
5. Fratta W., Biggio G. and Gessa G. L.: Homosexual mounting behavior induced in male rats and rabbits by triptophan free diets. *Life Sci.* **21** (1977) 379–384.
6. Grabowska M.: Influence of quipazine on sexual behavior in male rats. In *Sexual Behavior: Pharmacology and Biochemistry* (Edited by M. Sandler and G. L. Gessa). Raven Press, New York (1975) p. 59.
7. Baum M. J. and Starr M. S.: Inhibition of sexual behavior by dopamine antagonist or serotonin agonist drugs in castrated male rats given estradiol or dihydrotestosterone. *Pharmac. Biochem. Behav.* **13** (1980) 57–67.
8. Ahlenius S., Larsson K. and Svensson L.: Further evidence for an inhibitory role of central 5-HT in male rat sexual behavior. *Psychopharmacology* **68** (1980) 217–220.
9. Jacoby J. H., Poulakos J. J. and Bryce G. F.: On the central anti-serotoninergic actions of cyproheptadine and methysergide. *Neuropharmacology* **17** (1978) 299–306.
10. Morales A., Surridge D. H. and Marshall P. G.: Yohimbine for treatment of impotence in diabetes. *New Engl. J. Med.* **305** (1981) 1221–1222.
11. Sicuteri F., Del Bene E. and Anselmi B.: Aphrodisiac effect of testosterone in Parachlorophenylalanine-treated sexually deficient in man. In *Sexual Behavior: Pharmacology and Biochemistry* (Edited by M. Sandler and G. L. Gessa). Raven Press, New York (1975) p. 335.
12. Benkert O.: Clinical studies on the effects of neurohormones on sexual behavior. In *Sexual Behavior: Pharmacology and Biochemistry* (Edited by M. Sandler and G. L. Gessa). Raven Press, New York (1975) p. 297.
13. Bara R., Ambrosi B., Travaglini P. Elli R., Rondena M., Moriondo P., Gaggini M. and Faglia G.: Effetti del trattamento con agenti antiserotoninergici in pazienti con impotenza sessuale. *Atti XVII Congresso Nazionale S.I.E.* (1978) Abstr. C 180.
14. Malmnas C. O.: Monoaminergic influence on testosterone-activated copulatory behavior in the castrated male rats. *Acta Physiol. Scand.* (Suppl. 1) (1973) 395.
15. Tagliamonte A. Fratta W., Del Fiacco M. and Gessa G. L.: Evidence that brain dopamine stimulates copulatory behavior in male rats. *Riv. Farm. Terap.* **4** (1973) 177–181.
16. Hyyppa M., Rinne O. K. and Sonnine V.: The activating effect of L-Dopa treatment on sexual functions and its experimental background. *Acta Neurol. Scand.* **43** (1970) 223–224.
17. Wass J. O. H., Thorner M. O., Morris D. V., Ress L. H., Stuart-Mason A., Jones A. E. and Besser G. M.: Long-term treatment of acromegalic with bromocriptine. *Br. Med. J.* **i** (1977) 875–878.
18. Frajese G., Rocco A., Falaschi P., Pompei P. and D'Urso R.: Reproductive parameters in prolactinaemic men. *Arch. Androl.* **10** (1983) 179–183.
19. Frajese G., Mencacci Amalfitano M., Magnani A., Polimeni A. and Nerozzi D.: Neurochimica cerebrali e correlati endocrini della sessualità maschile. In *Progressi in Andrologia Chirurgica* (Edited by G. D'Ottavio and D. Pozza). *Acta Med. (Roma)* (1987) p. 151.
20. Frajese G., Falaschi P., Sciarra F., Rocco A. and Conti C.: Seminal fluid alterations due to metoclopramide-induced hyperprolactinaemia in man. In *Recent Progress in Andrology* (Edited by A. Fabbrini and E. Steinberger). Academic Press, London (1978) p. 421.
21. Frajese G., Rocco A., Sciarra F., Casacchia M., Meco G., Carchedi F. and Falaschi P.: Studio sulla funzione testicolare in corso di trattamento con neurolettici in soggetti psicotici. *Atti IV Simposio Int. "Applicazioni delle tecniche radioisotopiche in vitro"* (1977) 281–287.
22. Gessa G. L., Falaschi P., Rocco A. and Frajese G.: The role of brain dopamine in the regulation of ejaculation in male rats and men. *Proc. VI Int. Congr. Endocrinology* (1980) S–136.
23. Frajese G.: Dopaminergic and serotoninergic control of male impotence: management implications. In *Post-graduate Course Proceedings of A.S.A.*, Grand Rapids, Mich. (1986) 25–31.
24. Ahlenius S., Larsson K. and Svensson L.: Stimulating effects of lisuride on masculine sexual behavior of rats. *Eur. J. Pharm.* **64** (1980) 47–51.
25. Baggio G. and Ferrari F.: The role of dopaminergic receptors in the behavioral effects induced by lisuride in male rats. *Psychopharmacology* **80** (1983) 38–42.
26. Hlinak Z., Madlafousek J. and Krejci I.: Effects of lisuride on precopulatory and copulatory behavior of adult male rats. *Psychopharmacology* **79** (1983) 2–3.
27. Ahlenius S. and Larsson K.: Lisuride, LY-141865, and 8-OH-DPAT facilitate male rat sexual behavior via a non dopaminergic mechanism. *Psychopharmacology* **83** (1984) 330–334.
28. Lieberman A.: Pergolide and lisuride in advanced Parkinson's disease. *Adv. Neurol.* **40** (1984) 503–507.
29. Ruilope L., Garica-Robles R., Paya C., Morales J. M., Parada J., Sancho J. and Rodricio J.: Influence of lisuride, a dopaminergic agonist, on the sexual function of male patients with chronic renal failure. *Am. J. Kidney Dis.* **5** (1985) 182–185.
30. Horowski R.: Influence of ergot derivatives on prolactin secretion in rats. Mechanisms of action and clinical implications. *Cephalalgia* **3** (1984) 131–138.
31. Pfaff D. W.: Interactions of steroid sex hormones with brain tissue. Studies of uptake and physiological effects. In *The Regulation of Mammalian Reproduction* (Edited by J. Segal). Thornal, Springfield, Ill. (1973) p. 5.
32. Klotz H. P.: Testosterone and sexuality. *Horm. Res.* **18** (1983) 144.
33. Paup D. C., Mennin S. P. and Gorski R. A.: Androgen and estrogen-induced copulatory behavior and inhibition of LH secretion in the male rat. *Horm. Behav.* **6** (1975) 35–46.
34. Baum M. and Starr M.: Inhibition of sexual behavior by dopamine antagonist or serotonin agonist drugs in castrated male rats given estradiol or dihydrotestosterone. *Pharm. Biochem. Behav.* **13** (1980) 57–67.
35. Baum M. J., Canick J. A., Erskine M. S., Gallogher C. A. and Shim J. H.: Normal differentiation of masculine sexual behavior in male ferrets despite neonatal inhibition of brain aromatase or 5-reductase activity. *Neuroendocrinology* **36** (1983) 277–284.
36. Benkert O., Witt W., Adam W. and Leitz A.: Effects of testosterone undecanoate on sexual potency and the hypothalamic pituitary gonadal axis of impotent males. *Arch. Sex. Behav.* **8** (1979) 471–479.
37. Cautela J. R.: *Behavior Analysis Forms for Clinical Intervention*. Research Press, Ill. (1982).
38. Dahlstrom W. J., Welsh G. S. and Dahlstrom M. L. E.: *An MMPI Handbook*. University of Minnesota Press, Minn. Vol. 1 (1972).
39. Wiener D. H. and Harmon L. R.: Subtle and obvious keys for the MMPI: their development. Regional Veterans Administration Office, Mineapolis, Bulletin 16 (1946).
40. Welsh G. S.: A factor study of the MMPI using scales with item overlap eliminated. *Am. Psychol.* **7** (1952) 341–342.

41. Adams D. K. and Horn J. A.: Nonoverlapping keys for the items of MMPI scale. *J. Consult. Psychol.* **29** (1965) 284–287.
42. Harris R. E. and Lingoes J. C.: *Subscales for the MMPI: An Aid to Profile Interpretation. Mimeographed Materials.* Department of Psychiatry, Univ. of California (1955, corrected version 1968).
43. Pepper L. J. and Strong P. M.: Judge Mental Subscales for the MF Scale of the MMPI. Unpublished (1958).
44. Gough H. G. and Heilbrun A. B.: *Manual of Adjective Check List.* Consulting Psychologists Press, Palo Alto, Calif. (1970).
45. Plotsky P. M.: Facilitation of immunoreactive CRF secretion into the hypophysial-portal circulation after activation of catecholaminergic pathways or central norepinephrine injection. *Endocrinology* **121** (1987) 924–930.
46. Rivier C. and Vale W. W.: Modulation of stress induced ACTH release by CRF, catecholamines and vasopressin. *Nature* (1983) 305–325.
47. Smythe G. A., Bradshaw J. E. and Vining R. F.: Hypothalamic monoamine control of stress-induced ACTH release in the rat. *Endocrinology* **113** (1983) 1062.
48. Soliman F. A., Mash D. C. and Walker C. A.: The effect of altered 5-hydroxytryptamine levels and beta-endorphin content in rat brain (42326). *Proc. Soc. Exp. Biol. Med.* **182** (1986) 187–193.
49. Van Loon G. R. and Souza E. B.: Effects of beta-endorphin on brain serotonin metabolism. *Life Sci.* **23** (1978) 971–978.
50. Yaksh T. L. and Tyce G. M.: Microinjection of beta-endorphin into the periaqueductal gray evokes the release of serotonin from the spinal cord. *Brain Res.* **171** (1979) 176–181.
51. Haubrich D. R. and Blake D. E.: Modification of serotonin metabolism in rat brain after acute or chronic administration of morphine. *Biochem. Pharmac.* **22** (1973) 2753–2757.
52. Guillemin R.: Peptides in the brain: the new endocrinology of the neuron. *Science* **202** (1978) 390.
53. Mayerson B. J. and Terenius L.: β-endorphin and male sexual behavior. *Eur. J. Pharmac.* **42** (1977) 191–192.
54. Jaffe J. H. and Martin W. R.: Opioid analgesics and antagonist. In *The Pharmacological Basis of Therapeutics* (Edited by A. Goodman Gilman, L. S. Goodman and A. Gilman). MacMillan, New York (1980) p. 501.
55. Gessa G. L., Paglietti E. and Pellegrino-Quarantotti A.: Induction of copulatory behavior in sexually inactive rats by naloxone. *Science* **204** (1979) 203–205.
56. McIntosh T. K., Vallano M. L. and Barfield R. J.: Effects of morphine, beta-endorphin and naloxone on catecholamine levels and sexual behavior in the male rat. *Pharm. Biochem. Behav.* **13** (1980) 435–441.
57. Allen D. L., Renner K. J. and Luine V. N.: Naltrexone facilitation of sexual receptivity in the rat. *Horm. Behav.* **19** (1985) 98–103.
58. Holmes H. and Rahe R. H.: The social adjustment rating scale. *J. Psychosom. Res.* **11** (1967) 213–218.