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Sex, Migraine and Serotonin Interrelationships[1]

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The most popular links between sex and migraine are menstruation and pregnancy; these conditions can, respectively, precipitate and dispel headache attacks. Moreover, a history of migraine frequently starts from menarche and can strongly change at the moment of menopause. Another sex-migraine link appears in the area of sexual stimulation and intercourse. It is not rare, particularly in women, to have sexual excitation during the day (or hours) which precedes the migraine attack. The 'day-after' headache, that is, an attack on the day following sexual intercourse, is also frequent. The migraine sex interrelation is of particular interest in light of the monoamine central theory of migraine (14, 16). According to this theory, pain and other satellite phenomena originate in the brain, and they must be considered as a consequence of the imbalance of turnover concentration of monoamines, especially 5-hydroxytryptamine (5-HT). Because of the implication of monoamines, in particular 5-HT, on central sexual regulation, the reciprocal influence between sex and migraine, even if still obscure, should be discussed.

Many conditions (allergy, emotion, sex, sleep, etc.) may modify essential headache (EH): this phenomenon appears quite difficult to interpret. Some definitions, such as allergic, psychic, menstrual, hypnagogic headaches, can be considered only as convenient clinical terms, since, *per se*, such denominations are nonsense. Headache merits an exact nosologic collocation, because it is the most common expression of central dysnociception due to a derangement of the function of monoamines. 5-HT is of particular importance as a pain modulating-inhibiting agent in the brain. In other words, the central nociception, as any other function, is liable to a biochemical derangement, and obviously the clinical expression of this derangement cannot be anything but central pain. Since cen-

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tral nociception is apparently controlled by monoamines, 5-HT in particular, we first suggested that 5-HT might be the principal protagonist of EH (15). It is difficult to imagine a derangement of monoamines that is restricted to exactly the same area as that assumed to assimilate pain. It is most probable that a lesion of serotonergic neurons will implicate other ancestral functions such as sex, sleep, emotion, etc. Conversely, these latter monoaminergic functions may influence the nociceptive function, particularly if this function is genetically precarious and fragile, as is hypothesized in EH. In fact, the community of the same mediators, and the numerous integrations and interconnections among various ancestral functions, can explain the involvement of different nervous activities in EH only if one accepts the unitary monoamine central theory.

An EH attack frequently precipitates before, during, and/or after menstruations, and more rarely, at ovulation. It is clear that sex events catalyze the crisis, and this happens only in women with personal and/or a family history of EH. We cannot forget that migraine attacks in females are indistinguishable from those in males. The association between the fall of plasma estrogen (and not progesterone) and migraine attack, occasioned by a menstrual crisis, has been stressed recently. On the other hand, the modification of monoamine turnover observed in animal experiments during estrus (6, 7, 10) are of major importance; in fact, the central monoamine regulation of the estrus can be related to the role which 5-HT plays in modulating pain assimilations at the brain level (8, 22).

In their turn, animal and human observations must be considered in the light of the lowering of the pain threshold during the menstrual period, according to an ultradian biorhythm (11). Miscellaneous clinical phenomena (such as psychic tension, frank depression, insomnia, and fluid retention in the premenstrual period) indicate an involvement of the nervous function, particularly of the limbic system, in this period. One may hypothesize that the fluctuations in brain monoamine turnover during the menstrual period provoke the lowering of the pain threshold in several subjects. In EH sufferers, with a precarious brain monoamine balance, the menstrual biochemical changes can reach a critical level and precipitate the attack (14). In any case, it is of interest that even women with EH attacks at different moments of the month, usually feel that their most violent crisis occurs during the menstrual period. By considering the rhythmic physiological involvement of brain monoamines in the fecund period of women, one can understand the appearance or worsening of migraine during menarche and its disappearance at menopause. In pregnancy, an indirect evidence of brain monoamine involvement also could be considered: usually EH disappears at the 3rd month of pregnancy. It is a common observation that a women enjoys a striking well-being during pregnancy: particularly the ancestral functions, such as appetite, sleep, mood, etc., are normalized, if previously disrupted. Among these ancestral functions, it is more than rational to include nociception. On the other hand, in some pregnant women, a deterioration of the trophotropic functions,

such as nausea, vomiting, insomnia, anxiety, and/or depression clearly appears: in these subjects, a preexistent headache usually interacts with the side effects of pregnancy. While the brain monoamine involvement in occasion of pregnancy may be only hypothesized in humans, in animals (mice) brain monoamine levels fluctuate, particularly during estrus (7) and during the immediate postpartum period (6). The acute, and even more so the chronic administration of estrogen and progesterone influence the monoamine levels in the brain of ovariectomized rats (23). The regulation of estrous behavior in rats appears to be controlled by a serotonin-dependent inhibitory mechanism (10).

The main interrelationship between EH and sex can therefore be described as follows: (a) possibility of unusual sexual excitation ('sexual aura') during the day or hours which precede the migraine attack; (b) possibility of an EH crisis on the day which follows sexual intercourse; some patients tend to refuse a sexual relationship in order to avoid a migraine attack, and (c) possibility of a deterioration of sexuality, until complete impotence or frigidity, in patients with serious EH.

Our group has recently approached this problem of sexuality and EH through a clinical pharmacological exploration, assuming a close relation between migraine and sex. Our results have significance beyond the confines of the original problem, and now they suggest a new therapeutic approach to some derangements of sexuality.

As previously reported (16, 18, 19), our clinical pharmacological investigations can be summarized as follows: (a) in 3 male patients suffering from serious headache and complaining of hypersexuality, the administration of *L*-tryptophan (2–4 g/day) or *L*-5-hydroxytryptophan (200–600 mg/day) for a 6-month period, improved headache and corrected either completely (in 2 cases) or almost completely in 1 case, their hypersexuality. All the patients had previously been subjected to sedative treatments with tranquillizer drugs and psychotherapy with poor results (fig. 1).

5-HT precursors have been suggested in the treatment of the background migraine, improving the clinical picture or facilitating the action of conventional drugs, such as methysergide or pizotiphene (14). Lysergic derivatives, such as LSD-25, methysergide, and ergotamine, when administered in clinical doses, are not able to inhibit 5-HT; on the contrary, they potentiate 5-HT activity when the vein substrate (venoconstriction test) is used in man *in vivo* (20). These results have been confirmed in animals (3, 12, 13).

Parachlorophenylalanine (PCPA), a 5-HT depletor, when given in normal subjects does not modify their sexual behavior (1). On the other hand, in 6 out of 35 headache sufferers, a slight yet definite aphrodisiac effect is reported. In a woman, the sexual excitation was so remarkable and so unpleasant that it forced the discontinuation of PCPA administration. The difference between normal and EH sufferers as regards the aphrodisiac effect of PCPA lacks interpretation:

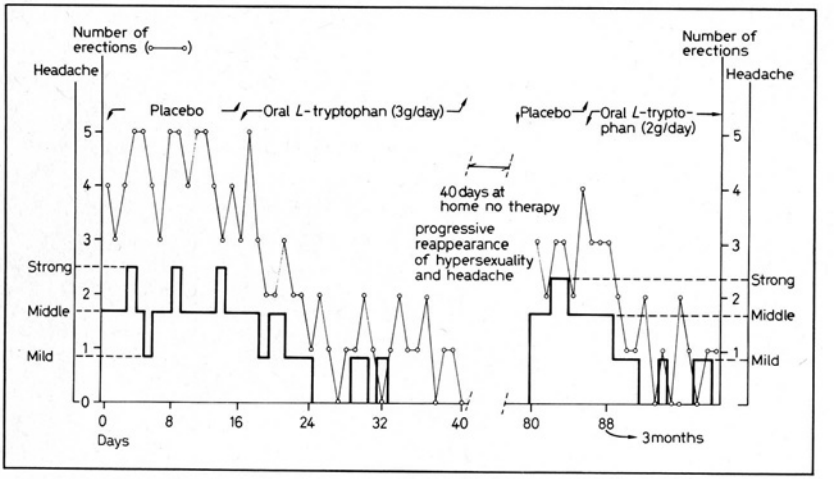

Fig. 1. The effects of *L*-tryptophan ingestion in a sufferer of hypersexuality and daily headache.

hypothetically, it could support the labile 5-HT turnover and brain concentration in EH sufferers (17).

In 16 headache sufferers with partial or total sexual deficiency, the administration of testosterone (25 mg/day, by injection) at the 5th to 7th day of PCPA treatment, provoked a frank sexual stimulation, with erections, vivid imagination, erotic dreams and the possibility of normal intercourse in at least 50 % of the cases. It is important to note that these patients were treated previously with testosterone or other drugs and/or with psychotherapy, with little or no result.

A control study with placebo, PCPA, and testosterone given separately or together, confirmed the above described aphrodisiac effect (fig. 2).

Two cases with complete impotence, and a strong reduction of testosterone plasma levels (19), as a consequence of abdominal aorta obstruction, and of postparotitic testicular atrophy, respectively, did not benefit from PCPA treatment.

The subsequent association of testosterone with PCPA provoked a clear aphrodisiac effect, with the reappearance of erections and the possibility of intercourse. EH sufferers, treated with PCPA, with or without sexual improvement exhibited normal testosterone plasma levels. The benefit on sexuality was maintained in some cases for some weeks or months after the discontinuation of the treatment. In some patients, following a reappearance of impotence, the readministration of PCPA plus testosterone was usually beneficial.

These observations on the whole, suggest that PCPA acts by depleting brain 5-HT, intended as a sex-inhibiting mediator at the level of the mating centers in

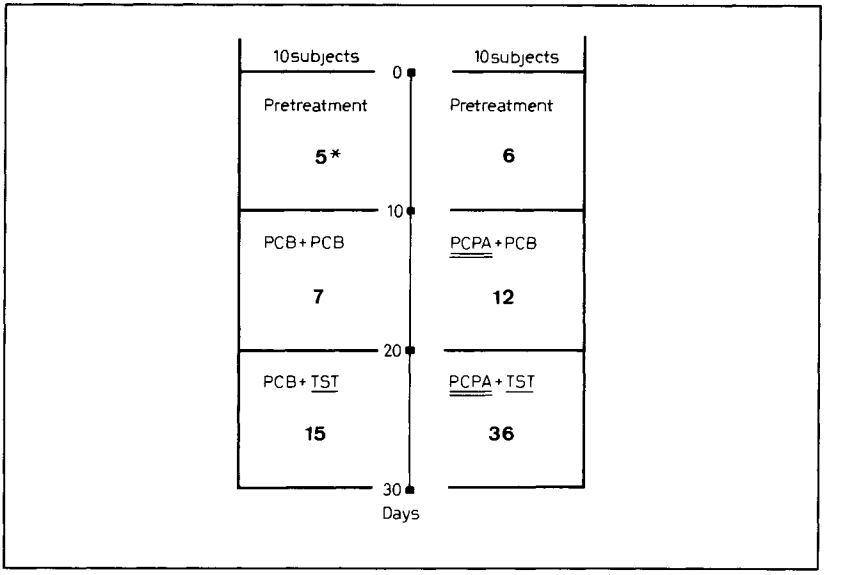

Fig. 2. A comparison between the effects elicited by testosterone and those by testosterone plus PCPA on sexual deficiency in an open clinical trial (number of penile erections). TST = Testosterone; PCB = placebo treatment in hyposexuality; * = number of erections.

the brain; the mating centers, sensitized by 5-HT depletion, are further stimulated by increased hormonal levels following testosterone administration.

It is known that the imbalance, more than a change in the concentration of a single monoamine (increased turnover of one and decreased of another) of two monoamines (5-HT and noradrenaline) is capable of affecting a nervous function. Thus, we have treated 8 volunteers, EH sufferers with deficient or absent sexuality with PCPA during 20–30 days; a few days afterwards a monoamine oxidase inhibitor (phenelzine or pargiline in usual clinical doses) was also administered. The PCPA plus MAO inhibitors treatment also exhibited a clear aphrodisiac effect in 4 of 7 treated patients; this effect was similar to that observed in PCPA-testosterone patients. Testosterone plasma levels remained unchanged. The MAO inhibition was controlled by the increase of urinary tryptamine excretion and by the reduction to zero of platelet MAO activity, evaluated by using double substrates, that is, ^{14}C-benzylamine and ^{14}C-tyramine (9).

Together with sexual improvement, an impressive benefit on the mood of the patient (apparently superior to that showed in PCPA plus testosterone treated patients) was also observed. It is impossible to determine whether the enhancement in mood is a consequence of sexual improvement, or a mere MAO inhibitor effect, or finally whether it is due to the strong monoamines (5-HT and catecholamines, dopamine in particular) shift with a decrease of 5-HT and an

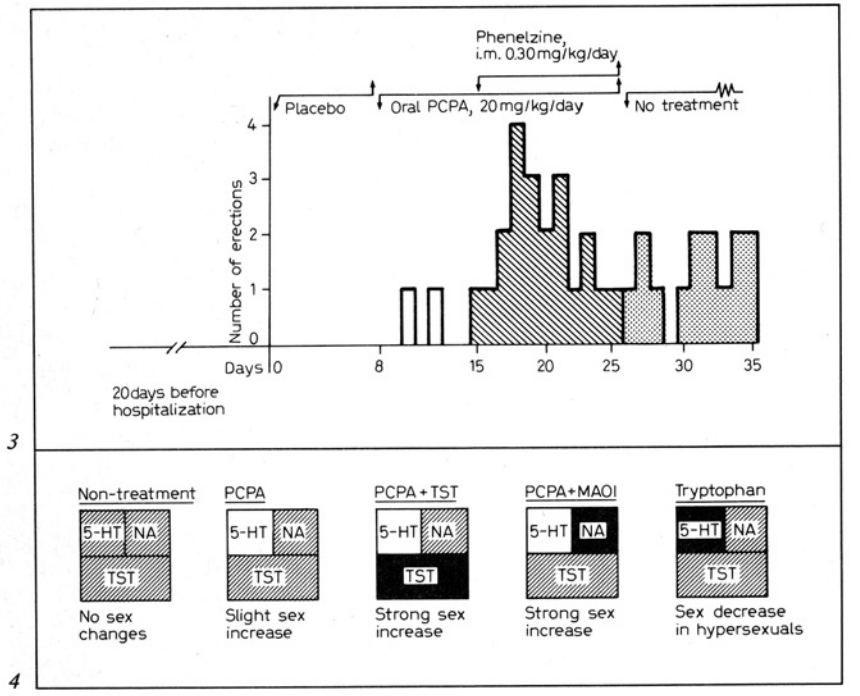

Fig. 3. The reappearance of penile erections following *p*-chlorophenylalanine and monoamine oxidase inhibitor administration in a headache sufferer with sexual deficiency.

Fig. 4. Possible interreactions among plasma testosterone, brain monoamine and correlated drugs in sexuality.

increase of catecholamine brain levels provoked just by MAO plus PCPA treatment. However, the PCPA-MAOI treatment seems particularly suitable in aging patients, where testosterone administration can be criticized for its prostate carcinogenic risk. In 3 of these 5 patients, the sexual benefit was maintained for 1–3 months. The repetition of the treatment was followed by aphrodisiac effect (fig. 3).

In sexually normal volunteers, the PCPA-testosterone (3 cases) and the PCPA-MAO inhibitor treatment (3 cases) failed to provoke a frank sexual stimulus.

Animal investigations (rats, rabbits, cats, etc.) (2, 4, 5, 21) are in agreement with the present studies. Castrated animals do not show sexual excitation after PCPA treatment; yet they become strongly stimulated when testosterone or MAO inhibitors are added to PCPA (5, 21).

It has been discussed whether the animal pharmacological hypersexuality is apparent, or whether it is rather an expression of a general hyperactivity, since

the animal, in its sexual approach, is not able to distinguish the sex of his partner (24).

In human investigations, we have not had this impression, because our patients when questioned about their sexual orientation did not experience hesitation from their effective or potential partner. On the other hand, we lack experience in dealing with sexually deviated subjects.

The multiple side effects of the drugs used – PCPA, testosterone, MAO inhibitors – suggest the maximum of caution, not only as far as concerns the treatment itself, but also as regards publicizing the present preliminary results. The present results are presented simply as a new approach to the interpretation and as a possible treatment of sexual derangement by modifying the brain monoamines pharmacologically (fig. 4). It is clear that much more clinical investigation should be carried out to clarify this question.

Summary

Sexual deficiency or frank impotence in man could be due to an imbalance of monoamines, particularly 5-HT, at the mating center level. An absolute or relative excess of 5-HT seems to antagonize testosterone at the level of the mating center receptors in the brain. Plasma testosterone levels in so-called psychological impotence are normal. When the 5-HT concentration in sexually deficient men is sufficiently decreased with parachlorophenylalanine (PCPA) treatment and testosterone levels increased following its administration, a vivid sexual stimulation appears in about half of the untractable cases. Similar results are observed by substituting testosterone with monoamine oxydase inhibitor (MAOI) in PCPA-treated volunteers. Furthermore, MAOI-PCPA are administered to emphasize the brain shift between serotonin and catecholamines. Yet the PCPA-MAOI treatment avoids the prostate carcinogenic risk of testosterone administration in aging males, and seems to have euphorizing effects stronger than those expected only from MAOI therapy. Because of the several side effects of PCPA-MAOI testosterone, the present experiments should be interpreted very cautiously.

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