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5-Hydroxytryptamine Supersensitivity as a New Theory of Headache and Central Pain: A Clinical Pharmacological Approach with p-Chlorophenylalanine

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Abstract. Vascular supersensitivity to 5-hydroxytryptamine, but not to noradrenaline is observed in volunteers suffering from untreatable migraine, following treatment with parachlorophenylalanine, a specific serotonin depletor. A similar supersensitivity at brain level is claimed to explain an unusual systemic pain syndrome developed in 4 patients affected by migraine and treated with this serotonin depleting agent; hyperalgesia, hyperpathia, spontaneous pain, according to the picture of central pain, are demonstrable. The pain syndrome is reversible with the drug discontinuation; it reappears promptly when the treatment is started again.

The pain from serotonin depletion may represent a chemical approach to the mechanism of central pain, such as thalamic syndrome, and may give a new suggestive light to the serotonin interpretation of migraine and some daily headaches.

The increased vascular and nervous responsitivity in patients suffering from migraine, to monoamines and correlated drugs (5-HT, noradrenaline, metaraminol, LSD-25 and psylocibine), may be interpreted in terms of central and peripheral monoamine supersensitivity.

Key words: 5-Hydroxytryptamine — p-Chlorophenylalanine — Central Pain — Supersensitivity — Essential Headache.

The enteramine (serotonin) theory of headache was proposed more than ten years ago, when metabolic changes of 5-hydroxytryptamine (5-HT) were observed during migraine attacks [16] and lysergic and non-lysergic antagonists of 5-HT were suggested and used successfully in migraine [10, 15]. In this connexion the observations on metabolic changes relating to 5-HT and the catecholamines in migraine attacks induced by nitroglycerin [1] and reserpine [3] were suggestive: when these drugs do not produce attacks in migraine, no changes of monoamine turnover are observable. Another suggestive datum is the monoamine oxidase defect on platelets in migraine: from this datum derives the possibility of considering migraine as an enzymatic disease involving monoamine turnover [17]. However, the involvement of 5-HT in migraine attacks is still to be demonstrated.

The main questions are the following:

1. Whether 5-HT is really implicated in the headache mechanism.

2. If so, where 5-HT plays its role: whether at the periphery (vessels) and/or at the center (nervous system).

3. Whether antiserotonins act independently of or through their specific action on 5-HT receptors.

4. If they act dependantly, where do the antiserotonins act, and how: in virtue of their known ability of antagonizing 5-HT at the periphery (microcirculation) or of their ability of mimicking 5-HT at the center (brain)?

It is in the aim of this paper to suggest a new theory, that headache and correlated phenomena are the expression of a deficiency of brain 5-HT with an ensuing central supersensitivity to monoamines. Amongst others, two recent observations support such a hypothesis:

a) Central pain syndrome from serotonin depletion follows treatment with p-chlorophenylalanine (fenclonine);

b) Central and peripheral hypersensitivity to amines and correlated drugs occur in sufferers from headache.

a) Central Pain Syndrome Caused by Fenclonine. Fenclonine inhibits the synthesis of 5-HT, but not of other amines, and consequently induces a specific selective depletion of brain and extra-cerebral serotonin [7].

During successful therapy of untreatable migraine with fenclonine[1] (0.8—1 g per day, orally: 1—6 months of treatment), in 4 of the 16 patients a systemic pain was complained of. Pain appeared, disappeared and again reappeared in a stereotyped way when treatment was discontinued and started again.

Particular superficial (skin) and deep (muscular) hyperalgesia was observed. The superficial hyperalgesia was striking in two cases; for instance the friction of sheets, stockings, and clothes was painful and sometimes unbearable. Similarly, to speak, to wrinkle the forehead or even to inspire deeply provoked pain; at the same time a slight fever was registered. No blood changes were observed, except eosinophilia in 3 out of 16 treated subjects: one of 4 patients with fenclonine pain syndrome had eosinophilia. 3 out of 4 subjects agreed to repeat the treatment from 1—4 times: each time the treatment provoked a painful syndrome with an increasingly shorter latency between the start of the drug administration and the first subjective phenomena. For instance in a patient (a woman 35 years old) who by her own accord repeated the treatment 4 times, the latencies were of 50, 30, 10 and 2 days

1 We are indebted to the Falorni Pharmaceutical Company (Florence) for the generous supply of p-chlorophenylalanine.

(Fig. 1). During the pain syndrome several pain tests were carried out: pricking, pinching, stimulation with radiant heat [9], test of stasis after ischemia [12], muscular exercise during ischemia [8], tests of cooling and heating. All these tests indicated clearly a superficial deep hyperalgesia, spontaneous deep pain, hyperpathia, according to the picture of the central pain.

The duration of the fenclonine pain syndrome varied according to the discontinuation of the treatment; from a minimum of 5 to a maximum of 30 days. This last duration occurred in the patient who first had this reaction during treatment at home: this 47-year-old woman did not keep contact with our staff. She insisted upon continuing taking the drug, and when a severe pain with complete disability appeared, the physician who fortunately contacted us, provisionally diagnosed a "very unusual muscular rheumatism" in view of the normality of the red-cell sedimentation rate.

b) Central and Peripheral Supersensitivity to Amines and Related Drugs. During the treatment with fenclonine, an increased constrictor sensitivity of the vein to 5-HT constantly appeared: the superficial vein of the back of the hand locally constricts (venoconstriction test) with doses from 2—5 times lower than those used before the treatment: in the patient with 4 repetitions of fenclonine administration during the painful phase, an impressive hypersensitivity (about 20 times) of the venomotor response appeared (Fig. 2). As it is known, this phenomenon may be likened to the hypersensitivity which appears following denervation: this denervation supersensitivity is attributed to the loss of agonist at the level of the receptors. In the venoconstriction test the increased sensitivity to 5-HT following fenclonine suggests an analogous phenomenon of supersensitivity. In fact this hypersensitivity, clearly correlated with fenclonine administration, is specific for 5-HT, vein contricting with adrenaline and noradrenaline as in basic conditions. A similar peripheral hypersensitivity appears during the migraine attacks [14], with the difference that the hypersensitivity concerns both monoamines, that is 5-HT and NA, and it lasts a few hours (Fig. 3).

In many patients with chronic daily headache an increased sensitivity of monoamine venomotor receptors is demonstrable [12]. The sensitivity could be considered as a pattern of sensitivity of the monoamine brain receptors.

Clinical pharmacological studies in patients with chronic headache or during attacks of migraine reveal, even if in different ways, a hypersensitivity to the administration of drugs which have to do directly or indirectly with amines and their turnover.

1. ergotamine: possibility of hyperemesis and peripheric vascular collapse during the migraine attack and not in the free period.

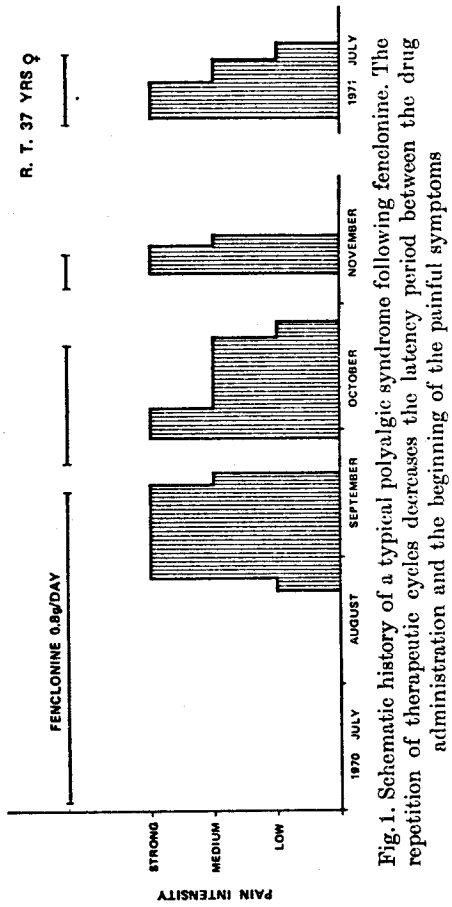


Fig. 1. Schematic history of a typical polyalgic syndrome following fenclonine. The repetition of therapeutic cycles decreases the latency period between the drug administration and the beginning of the painful symptoms

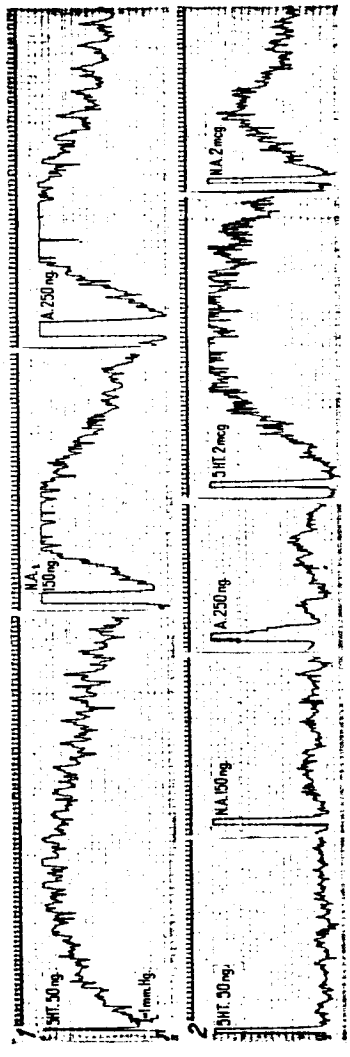
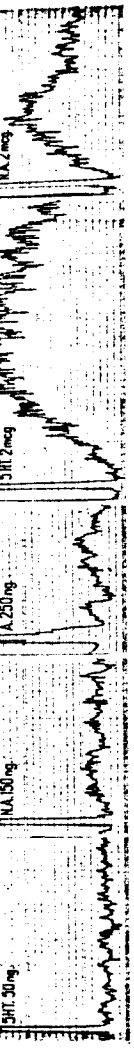


Fig. 3. Venoconstriction test 1) high venomotor sensitivity to 5-HT, NA and A in patients affected by migraine at the end of an attack. 2) Far from the attack the same doses of 5-HT, NA and A are inefficient and it is necessary to administer doses from 10—20 times higher to have an analogous venomotor response

2. methysergide: possibility of hyperemesis and peripheral vascular collapse during the migraine attack and not in the free period. Hallucinations, similar to those of LSD-25 are occasionally reported (3 personal observations).

3. LSD-25 and psylocibine: threshold of psychic reactions lowered in daily chronic headache [5] (Fig. 4).

4. Hypersensitivity to histamine (but not to other vasodilatators, e.g., papaverine) and to histamine liberator 48/80 during chronic daily headache and migraine attack.



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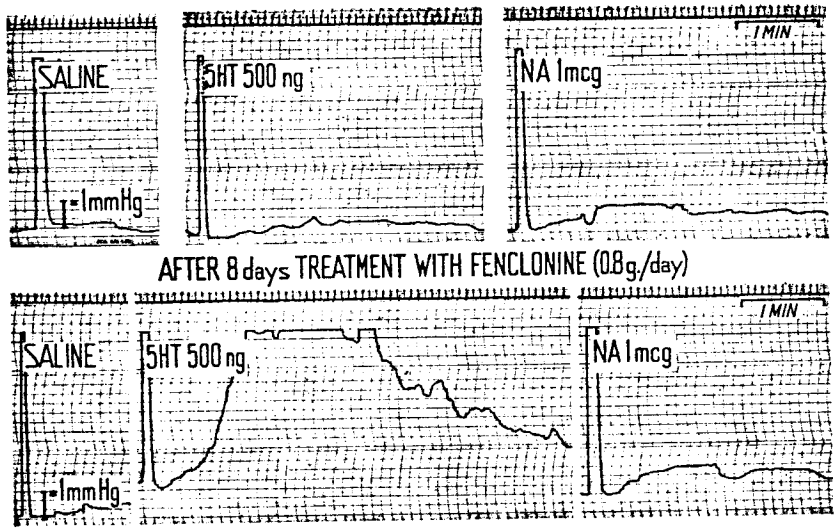

Fig. 2. Venoconstriction test—500 ng of 5-HT, unable to spasm the vein before treatment with fenclonine, after the treatment are efficient. NA sensitivity does not appear increased by fenclonine

5. Precipitation of the migraine crises or increase of daily headache following small doses of reserpine.

6. Hypersensitivity of conjunctival vessels to noradrenaline before the painful phenomena of the attack [19].

7. Hypersensitivity of the superficial vein of the back of the hand to 5-HT and noradrenaline during the migraine attack [14].

8. Metaraminol, in some cases of chronic headaches, administered orally in amounts that are 20 times lower than the clinical dose of 10 mg (1 drop instead of 20), may intolerably increase the headache. Such doses normally do not affect the blood pressure and the circulation [13].

9. Increase of the headache during the migraine attack, or in chronic daily headache following administration of bradykinin, kallidin, kallikrein (but not by eledoisin or physalaemin) [11].

Comment

5-HT seems to play a role as mediator in some nervous functions: it could be an inhibiting rather that an activating mediator. Phylogenetically primitive functions such as appetite, vomiting, fever, emotion, could be modulated by 5-HT. These functions are typically affected in the migraine attacks. Our observations support the hypothesis that pain, as a primordial function, is also under the control of serotonin. If the

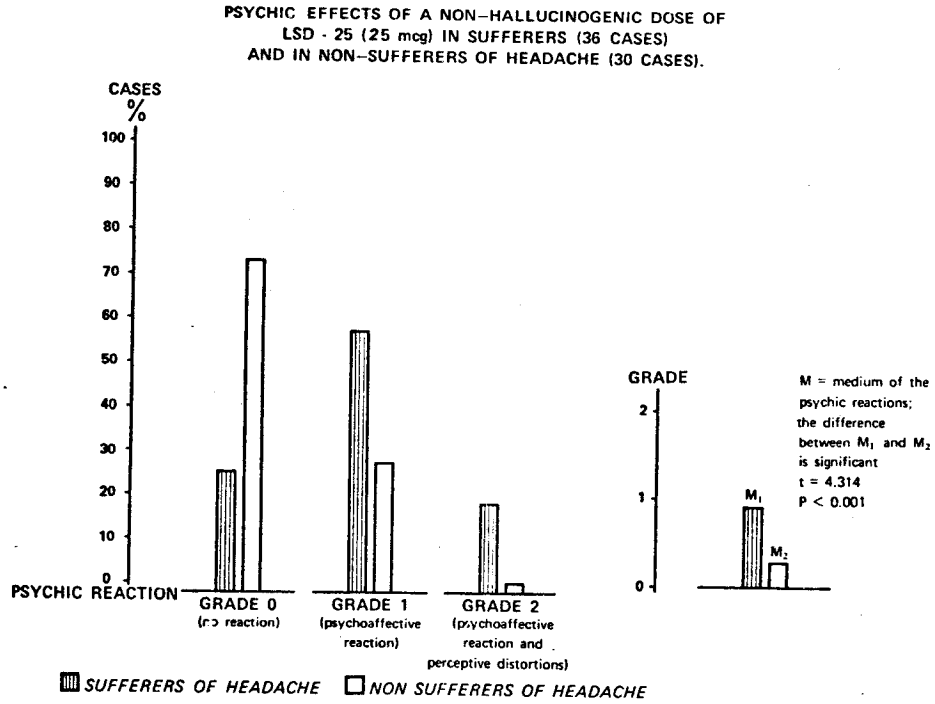

Fig. 4. Subjects suffering from headache result to be more sensitive than normal subjects to the psychic effects of a non-hallucinogenic dose of LSD-25. The difference between the averages of the psychic reactions of the two groups is highly significant (from Fanciullacci *et al.*, Relaz. Congr. Medicina Psicosomatica, Florence 1971—modified)

pain syndrome after fenclonine administration does not represent an unknown side-activity of the drug, but is correlated with its main action, it would constitute a highly suggestive support of this hypothesis. We may hypothesize that continuous painful impulses come from the periphery but their arrival to the perceptive area is prevented by a physiological serotonin concentration in the brain; when this sort of chemical barrier passes out, the pain impulses will get acrosst his barrier and will arrive at the level of the consciousness (Fig. 5).

In normal subjects [2] or in patients with intestinal carcinoid [4], syndromes not connected with pain have been observed during fenclonine treatment; the rather high incidence (25%) of pain reaction in our group of patients may depend on the duration of the treatment, on sex (mainly female in our observations) or more probably on the fact that all our cases are sufferers from headache.

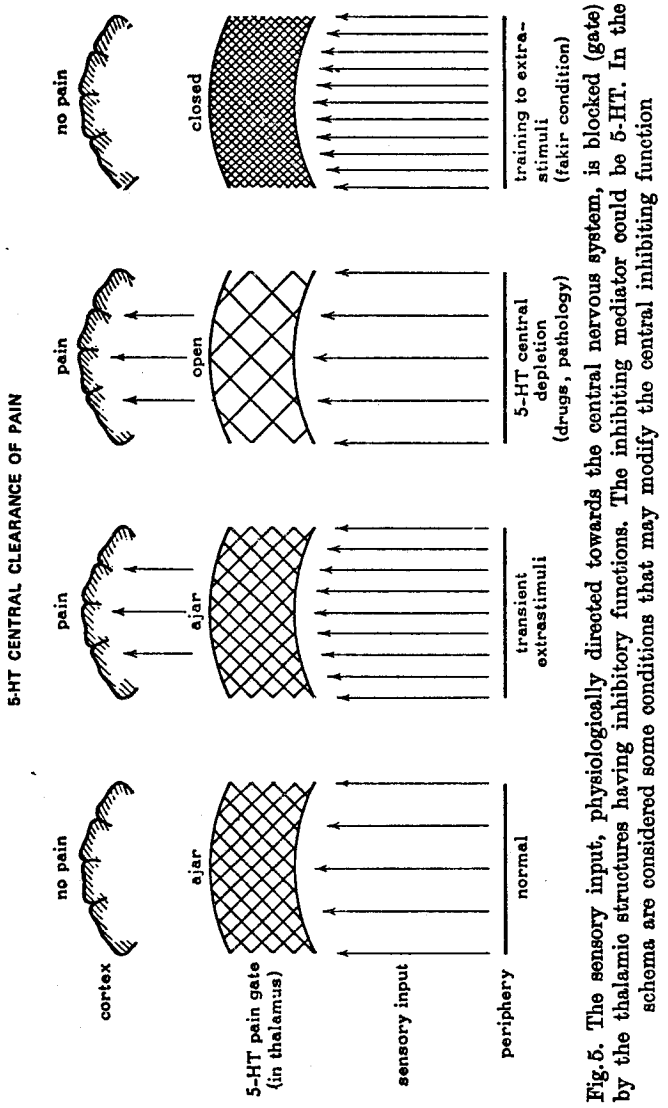

Fig. 5. The sensory input, physiologically directed towards the central nervous system, is blocked (gate) by the thalamic structures having inhibitory functions. The inhibiting mediator could be 5-HT. In the schema are considered some conditions that may modify the central inhibiting function

This may support further the idea that in headache some differences in the serotonin metabolism do exist.

Some observations suggest that in animals also fenclonine may produce pain, central in nature and correlated with brain serotonin depletion. Tenen [18] in 1967 observed that rats treated with fenclonine become irritable with handling. The pain test (jump threshold by

electric shock) indicated a lowering of the pain threshold. Administration of serotonin, (which does not pass the brain blood barrier) did not modify the hyperalgesia in the rat, while the serotonin precursor, 5-hydroxytryptophan, which does penetrate the barrier, was able to correct the hypersensitivity to painful stimuli. Also the reduction of total brain serotonin as obtained in rats through lesions of medial forebrain bundle, lowered the jump threshold to shock [6]. How can we correlate these clinical pharmacological observations on pain due to fenclonine with spontaneous human pathology? An analogy may be drawn to central pain in thalamic syndrome: a strong reduction of brain serotonin following traumatic or spontaneous (tumoral, vascular) lesions could be postulated as biochemical basis of pain. In headache such a proposal is more difficult to support; for instance it may appear incompatible with the efficiency of fenclonine in untreatable migraine. On the other hand some pictures of chronic daily headache (headaches with hyperalgesia of the scalp and of the neck, tendency to tiredness, often a slight fever, superficial and deep threshold lowering to painful stimula) are indistinguishable from a mild fenclonine pain syndrome. For migraine the situation is more intriguing: one may think of a defect and instability of the brain monoamine turnover in those areas in which they are usually concentrated and particularly in the sectorial area of the subcortical thalamic system where the head sensitivity is circumscribed. The attack may be connected with an acute decrease of monoamines, serotonin in particular. In other words, in chronic daily headache (some cases are chronic from the beginning, others are cases of migraine that have become chronic) the deficiency of serotonin seems chronic and quite stable. In migraine the monoamine decline occurs explosively and concerns not only the central sensory projection of the head, but also the emotional vegetative functions, modulated by monoamines (appetite, vomiting, sleep, fever, affectivity), all more or less clearly affected during the attack.

If one accepts that the central pain derives from a deficiency of serotonin, it remains quite difficult to understand whether this happens because the amine is scarce, or because a phenomenon of supersensitivity is present. We observe, during fenclonine administration in man, by using the venoconstriction test, the phenomenon of supersensitivity to 5-HT, but not to NA; so the possibility of a 5-HT supersensitivity, postulated also by others [6], may be imagined in central serotonin receptors. Thus, in this light the therapeutic activity of antiserotonin drugs may be reconsidered: if their action is connected to the antagonist activity, does it occur at the periphery (for example in the head vessels) or in the brain? Accepting the theory of a central deficiency (and therefore supersensitivity) to serotonin, are the antiserotonin drugs active

because they protect the hypersensitive receptors to serotonin or, acting as false mediators, do they take the place of the missing serotonin? In other words, in the light of this theory, it may be discussed whether the mechanism of migraine prophylaxis with antiserotonins is competitive or substitutive.

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