Serotonin Depletion Illness: A proposed condition — Dr N Lötter

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Curriculum vitae

Dr Nico Lötter was born in Bloemfontein in 1949. He received his MBChB from Stellenbosch University in 1973. Dr Lötter did his internship at the Ernest Oppenheimer and Natalspruit Hospitals. He was a Lieutenant SAMS as part of compulsory military service during which time he served on the border and in Angola, as second charge surgeon, and the rest of the time as Command Medical Officer, Witwatersrand. Dr Lötter has been in private practice since 1980.

Summary

In family practice more and more patients are presenting with symptoms of fatigue, down-moodedness, sleep disturbances and pain disorders. Multiple treatment regimes follow, and fail; much gets lost, especially the very important doctor-patient relationship. This paper thus suggests that Serotonin may be one of the substances that protect the human body from a noxious environment where sensory overload exhausts the synaptic vesicles of this important neurotransmitter. It describes the diagnosis of a proposed condition, Serotonin Depletion, illustrates its probable mechanism, gives suggested treatment and also its possible importance.

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KEYWORDS:
Physicians, Family; Burnout, Professional; Stress, Psychological; Serotonin; Neurotransmitters.

Introduction

In family practice today, an ever growing percentage of patients are presenting with characteristic disease patterns and symptomatology, that of fatigue, irritability, sleep disturbance, downmoodedness and a large variety of pain disorders. These are inexplicable by current medical teaching. There is a paucity of physical and laboratory findings to account for the gross nature of the complaints (this being the key to the hypothesized diagnosis) and often a defiance of cure after multiple treatment regimes, investigations and procedures involving major costs, lost man hours, serious socio-economic and behavioural deterioration and disability. All this leads to the deterioration of the all important patient/physician relationship, especially when conditions become labelled as psychogenic, psychosomatic, functional, stress-related and depression. Because of the epidemic proportions of this condition serotonin depletion is suggested as the common denominator.

Known Role of Serotonin

1. Modulation of pain.[1,2,3,4]
2. Maintenance of delta sleep.[1,3,4,5]

Proposed Additional Roles of Serotonin

1. Protection of immunity.[1]
2. Control of mood.[2,5]
3. Normalising hypothalamic endocrine control.[3,6]
4. Containment and resolution of inflammation.
5. Prevention of bronchospasm and allergic reactions.
6. Control of blood pressure, carbohydrate, lipid and protein metabolism.

Points 4, 5 and 6 are thought to occur by reducing the effect of stress on the hypothalamic-pituitary-adrenal axis.[7]

Neurophysiology

SDI (*Serotonin Depletion Illness*) is proposed as a central neurochemical disorder found mainly in urban

societies where an abundance of sensory input from outside and within (popularised as stress) exhausts the midline raphe nucleus in its synthesis and storage of serotonin.[5,8]

We are postulating that serotonin modulates adrenergic sensory conduction in the reticular activating system when secreted into synapses where both midline raphe nucleus and sensory neurons are present.[9] We suggest that serotonin binds to the postsynaptic membrane and changes protein molecules to alter permeability in the following manner:[10,11]

Immediate drastic reduction of analgesic abuse

1. With initial stimulation the postsynaptic membrane is permeable only to potassium, allowing potassium ions to efflux because of its Nernst or concentration potential and in the process hyperpolarising the membrane.[12] This increase in safety factor (action potential/excitability) will allow only strong and or meaningful impulses to cross and to be relayed to the sensory cortex.[13]

2. With increased stimulation the membrane becomes permeable to both potassium and chloride, inhibition of conduction will take place because an action potential will immediately be corrected by the freely diffusible potassium and chloride. This phenomenon is called clamping,[12] possibly resulting in excessive drowsiness and sleep because the reticular activating system fails to activate the cerebral cortex properly.

3. Increased sensory loading causes excessive secretion of adrenergic sensory neurotransmitters which possibly damage the postsynaptic membrane and also drain the accompanied serotonin secreting vesicles (which should have done the mending). This allows the larger sodium ions to become diffusible across the postsynaptic membrane resulting in hypopolarisation and excitability even to weak and/or meaningless sensory impulses. Irritability, hyperalgesia and sleep disturbances result. Furthermore, the sodium pump becomes exhausted and unable to restore membrane potentials, further hampering synaptic function and causing fatigue and vestibular malfunction.

The proposed reaction of sensory overload on the motor system is as follows:

1. Initial facilitated improvement due to hyperpolarisation.
2. Muscle weakness due to clamping.
3. Repetitive meaningless actions due to hypopolarisation (eg restless legs, pulling up shoulders, coarse tremor).

We postulate that sensory overload

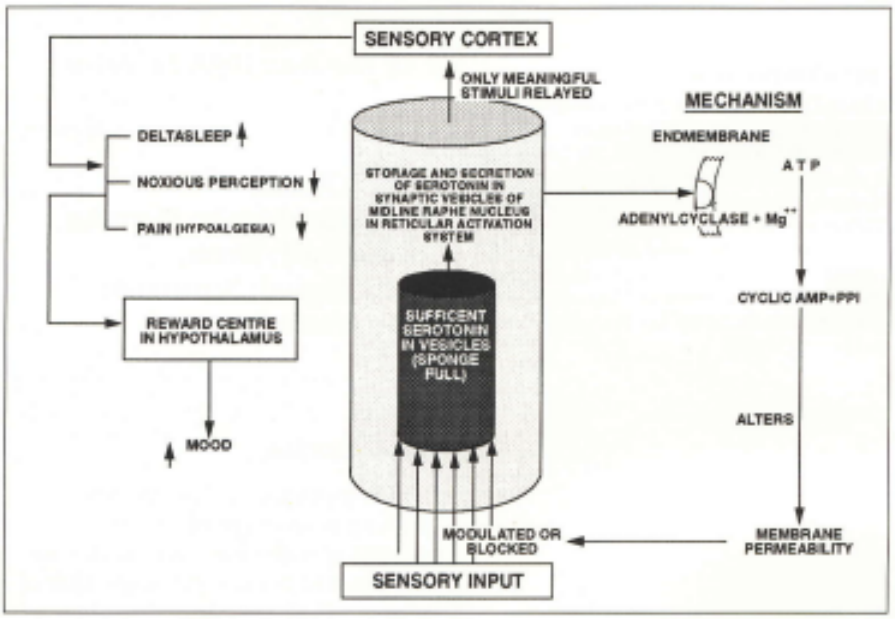

Diagram 1: Proposed Normal Sensory Control

The transmitter vesicles in the synaptic knobs from the midline raphe nucleus (MRN) are full, inhibiting the reticular activating system (RAS) with modulation of sensory input (pain and other perceptions). Deltasleep is also maintained with stimulation of the hypothalamic (HT) reward centre and elevation of mood.

with sleep disturbances fail to restore:

1. Neurotransmitters via presynaptic absorption.

2. Mitochondrial glycogen stores remain empty so that energy cannot be generated to drive the sodium pump with increasing motor weakness and fatigue.

Proposed Sequelae to Serotonin Depletion

1. In an effort to assist the depleted serotonin and as a result of direct stimulation of the hypothalamic aversion centre, especially the periventricular and the midline pre-optic areas, pre-opiocorten is synthesized and secreted as the precursor to endorphins and ACTH[14] (see Diagram 2). ACTH in turn stimulates cortisol production.

2. As a result of unmodulated sensory overload there is probably direct autonomic nervous system stimulation with both sympathetic and parasympathetic sequelae.[5, 15] (See diagram 3)

Treatment is aimed at upgrading the body's own neurochemical analgesia

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Sympathetic sphincter muscle spasm will cause dilatation of hollow vicus (eg bowel) resulting in spontaneous influx of calcium and sodium setting off an action potential experienced as cramp-like peristaltic pain.[1, 16, 17]

3. Another proposed sequelae of sensory overload and serotonin depletion is the development of pain due to muscle spasm.[15, 17, 18, 19] (See Diagram 5).

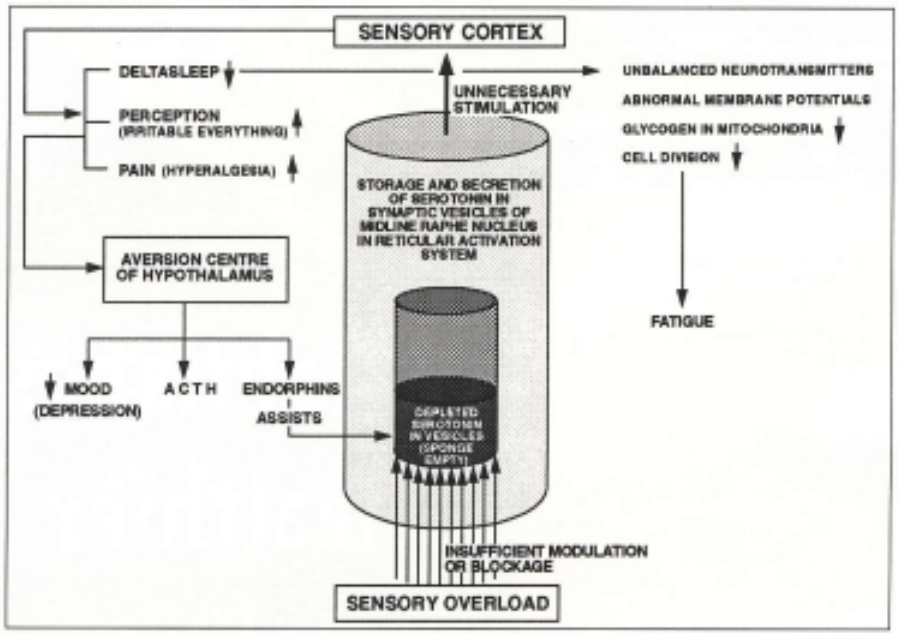

Diagram 2: Proposed Abnormal Sensory Control due to Serotonin overuse (Burn Out)

Insufficient serotonin allows an abundance of noxious stimuli to reach the conscious cerebral cortex with subsequent stimulation of the aversion centre, resulting in the synthesis of pre-opiocorten, the precursor of endorphins and ACTH. Note that a lack of deltasleep causes fatigue.

Diagnosis

Having met the characteristic major criteria of fatigue, irritability, sleep disturbance, pain disorders and downmoodedness, minor criteria include: flatulence, paraesthesia, subjective swelling, cold extremities, nausea, dizzy spells, burning feet, restless legs, catarrh, palpitations, tremor, tight chest and throat, neck stiffness, oliguria, irritable bladder, dyspnoea, pruritus ani, diarrhoea and/or constipation, reduced mental ability and behavioural alterations.

On Examination

Apart from generalized tender trapezius muscles and diffuse abdominal tenderness, trigger and/or tender points representing the tautness of muscle or tendon and leaving an area of cutaneous hyperaemia after palpation, will be found in uncannily constant anatomical areas as seen in Figure 1.[20, 21]

The whole constellation of signs and symptoms as described can be artificially produced by the injection of parachlorophenylalanine (a serotonin antagonist).[3, 5]

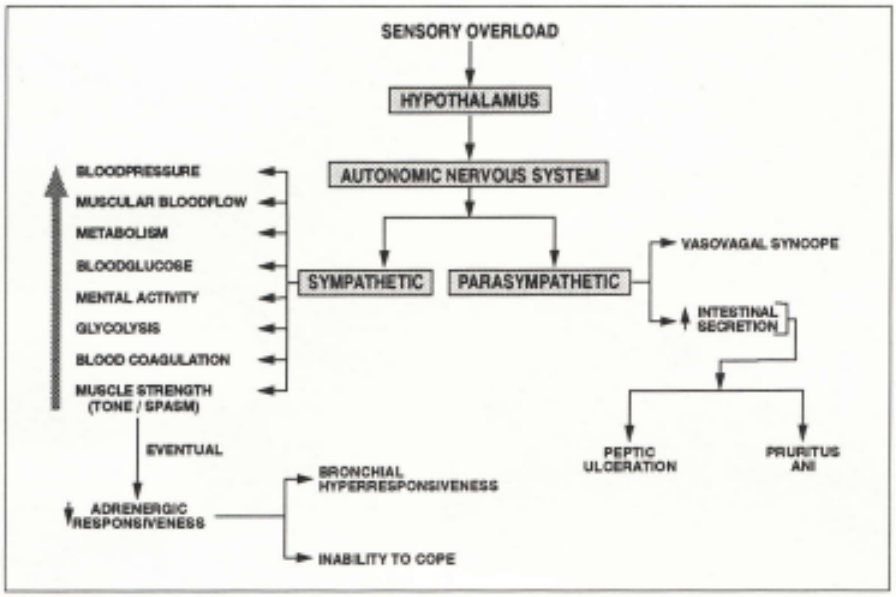

Diagram 3: Proposed Effects of Stress on the Autonomic Nervous System

Note that aversion centre stimulation results in both sympathetic and parasympathetic sequelae. Continued sensory overloading results in over activity of the autonomic nervous system with diminished receptor responsiveness. If a human body does not receive sympathy, downmoodedness will inevitably occur.

Laboratory Findings

Serotonin depletion is a clinical diagnosis, and laboratory investigations should only be done to rule out other conditions suggested by the patient's history and physical examination or in the case of treatment failure.

Treatment

Treatment is aimed at disruption of the painful reverberatory cycles and stimulation of endogenous opioids while restoring serotonin levels in the brain. Desensitisation of hyperalgesic nerve endings is important as well as the elimination of perpetuating factors. Immediate drastic reduction of analgesic abuse is essential since treatment is aimed at upgrading the body's own neurochemical analgesia which is crippled by the external intake of pain relieving compounds.[22]

Trigger and/or Tender Point Injections

5 - 10cc of 2% lidocaine is used to block the three reverberatory cycles (Diagram 5) and desensitise the hyperalgesic pain receptors.

Endogenous opioids are also secreted because of the so-called acupuncture effect.[6,15]

The therapeutic effect long outlasts the short acting lidocaine.[15,23] It is sometimes necessary to inject up to five trigger points at one session and this may be repeated a few times to obtain complete relief. A dosage of up to 400 mg lidocaine is very safe with the only side effects of lightheadedness, tinnitus and tongue numbness.[24]

A long acting hydrocortisone should be added to the lidocaine only if the co-existence of an inflammatory process is anticipated.

Intravenous Infusions of Serotonin Agonist

In an effort to replenish the hypothesized exhausted serotonin synaptic vesicles, amitriptyline in a low dose (20 - 40 mg) together with sulpiride (100 mg - to stimulate hypothalamic opioid production giving a potent synergistic action) in 50cc normal saline is infused intravenously over five to ten minutes in the consulting rooms on consecutive days until sedation is no longer experienced from the infusion (usually 3 to 5 days). It is of utmost importance not to refer to the medication as being an antidepressant as it will make the patient feel inadequate, rather refer to it as a neurotransmitter. The parental method is used for the following proposed reasons:

Refer to the medication as a neurotransmitter, and not as an antidepressant

1. Immediate results with resolution of symptoms is achieved due to

. . . Serotonin Depletion Illness

bolus infusion into the plasma, resulting in rapid crossing of the blood-brain barrier via the process of diffusion in the aquaeductus of Sylvius,[10, 25, 26, 27, 28] allowing the medicated cerebral spinal fluid to attend to the empty transmitter vesicles in the soma, dendrites and axons of the midline raphe nucleus. This overcomes labour abstinence, suicide, rages, as well as erratic bioavailability and the slow onset of oral serotonin agonists.[29]

2. Oral medication will be completely absorbed by the presumably dry synaptic vesicles in the medulla improving sleep but leaving the rest of the system unattended.[4, 10, 29]

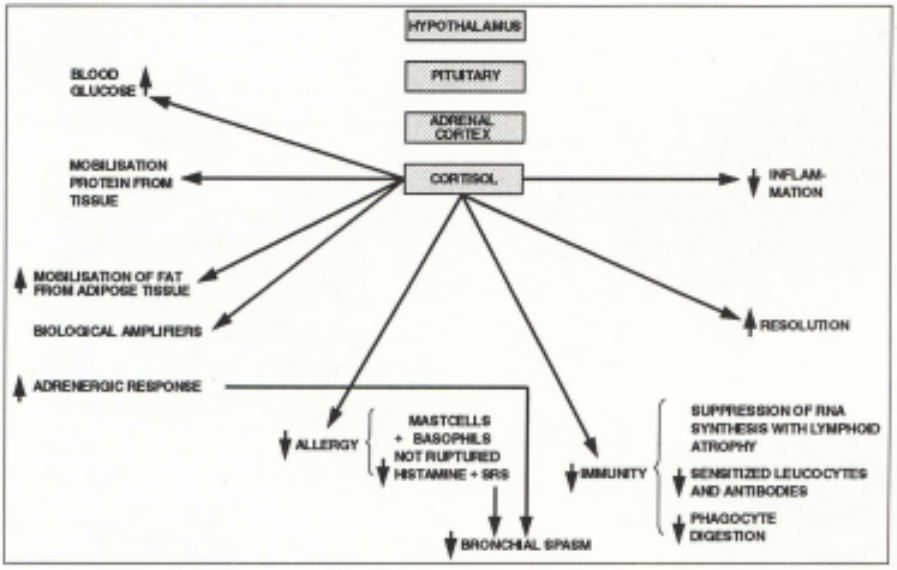

Diagram 4: Proposed Corticosteroid Function

Corticosteroid function as a result of sensory overload is suggested. The longterm effects:

1. ↑ Glucose, fat and proteins in blood.

2. ↓ *Immunity.*

Diagram 2 suggests the continuous syntheses of ACTH in the serotonin depleted human with a constant increase in cortisol secretion and a negative feedback on the axis. In a situation of acute stress (eg trauma, operation or infection) the cortisol response will be slow and inadequate resulting in:

1. ↑ *Inflammation.*

2. ↓ *Resolution of inflammation.*

3. ↑ *Bronchial hyperresponsiveness.*

4. ↑ *Reaction to allergens.*

On average three daily infusions results in excellent pain modulation, mood elevation, restoration of delta sleep and vitality after which the patient is kept on a low dose amitriptyline or another serotonin agonist for at least six months.

Hospitalisation

In our experience it has been found that admission to hospital for intravenous serotonin build up and/or sleep therapy is only required in the presence of acute distress from abnormally high sensory input, or in the presence of so-called perpetuating factors, in an effort to remove the patient from his habitat for treatment while urgently attending to the correction and elimination of causative factors.

Failure

Frequent re-occurrences or failure to respond, calls for an indepth investigation into perpetuating circumstances and thorough multidisciplinary consultation and special investigations.

Supplementation with magnesium, may be essential for optimum results.

General

Fitness from aerobic exercise, neck manipulation and daily stretching of

Serotonin Depletion is a clinical diagnosis; lab investigations only to rule out conditions suggested by the patient or where treatment fails

the trapezius muscles, physiotherapy, and stress management programmes are of the utmost importance.

Importance

If the role of serotonin is established to be as hypothesized, it will enhance the physician's ability to treat a host of conditions previously unresponsive to traditional methods. Patients presenting with the typical symptoms and signs of SDI can be effectively treated without a multitude of tests and consultations thereby decreasing medical costs.

To Conclude

The widely spoken of "burn-out", "lacking in the system", "all in the mind" and "nerve related", may refer to the neurochemical serotonin.

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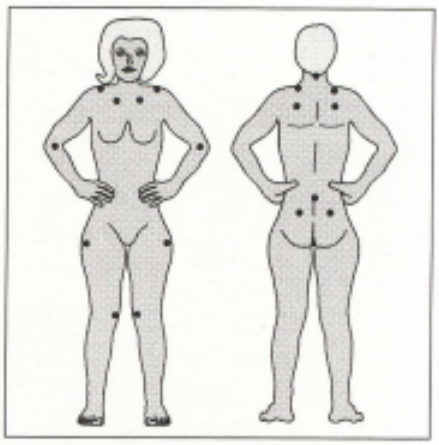

Figure 1: Eighteen Tender Spots

The unilateral sites are at the intertransverse and/or interspinous ligaments of C4 to C6 and the interspinous ligament at L4 to L5 and the bilateral sites at the upper borders of the trapezius, the supraspinatus origins at the medial border of the scapula, the upper outer quadrants of the buttocks, the second costochondral junctions, the lateral epicondyles of the elbows, the medial fat pads of the knees, proximal to the supraspinatus implantation at the shoulder and the area overlying the greater trochanters of both hip joints.

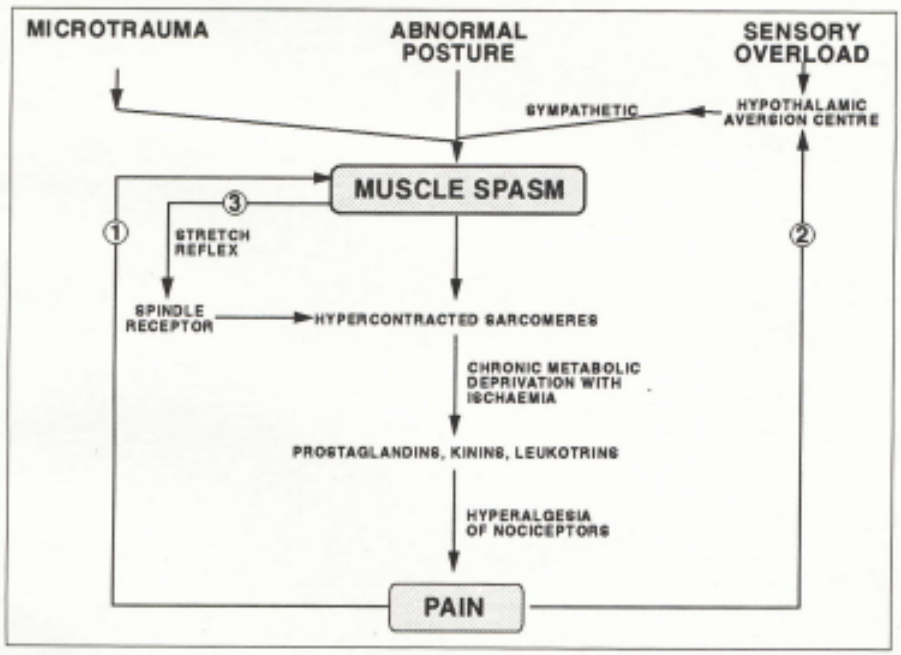

Diagram 5: Proposed Muscle Spasm Pain Reverbatory Cycles

Musclespasm after microtrauma, abnormal posture and sensory overload cause three reverberatory cycles as well as hyperalgesia of nociceptors.

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