Serotonin in the elderly

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Serotonin is said to determine our emotions, moods and affect. The physiology of serotonin implies it in the regulation of biological functions in line with our mood, like accelerated heart rate and sweating triggered by feeling flustered. Serotonin has multiple pharmacological actions in the body and alterations in serotonergic function may account for behavioural disturbances commonly observed in the elderly. The clinical effectiveness of selective 5-HT reuptake inhibitors (SSRIs) is believed to be mediated through enhancement of extracellular 5-HT. Various studies have shown that the SSRIs are better tolerated in older people compared with the tricyclic antidepressant or serotonin-norepinephrine reuptake inhibitors (SNRIs). It is obvious that serotonin plays a significant role in the emotional wellbeing of people – whether they are young or old and there are various ways of increasing serotonin in the body in order to create a feeling of wellbeing and content.

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Serotonin (5-Hydroxytryptamine)

Serotonin is commonly seen as a contributor to feelings of well-being and happiness. It basically determines our emotions, moods and affect. Mood is an affective state that differs from temperament or personality. It is not emotions or feelings that we have but has a positive or negative valence. A positive mood shows no stress and facilitates creative problem solving and careful, flexible thinking. A negative mood can manipulate how individuals interpret and translate the world around them and it can direct their behaviour. It also influences their judgement and perception of objects and events. The limbic system sits under the cerebrum and is the major primordial brain network underpinning mood. It regulates biological functions in line with our mood, like accelerated heart rate and sweating triggered by feeling flustered. The hypothalamus modulates hormones associated with mood and survival. It controls autonomic functions like sweating, heart rate, breathing and sleeping. The hippocampus reminds us which courses of action lead to outcomes that match our mood. It has been shown to be shrunken in people prone to depression. The amygdala attaches emotional significance to events and memories. Experiments where monkeys had their amygdalae removed showed them exhibiting bizarre patterns of behaviour: they became fearless, hypersexual and either devoid of emotion or aggressive.¹

The chemical structure, 5-Hydroxytryptamine (5-HT) is widely distributed in human beings and the animal and plant kingdoms. It is synthesised by a two-step pathway from the essential amino acid tryptophan. Its principal route of metabolism involves deamination by monoamine oxidase (MAO) to 5-hydroxyindole acetic acid (5-HIAA) which is excreted in the urine. It is actively transported into the brain by a carrier protein. The synthesised product, 5-HT, is stored in secretory granules and released by exocytosis from serotonergic neurons. Tryptophan hydroxylase is the rate-limiting enzyme in its synthetic pathway.

The pharmacology of serotonin

In essence, serotonin is a regulator of smooth muscle in the cardiovascular system and the gastrointestinal tract, an enhancer of platelet aggregation, and a neurotransmitter in the central nervous system (CNS) in human beings. Serotonin is found in high concentrations in enterochromaffin cells throughout the gastrointestinal tract, in storage granules in platelets and throughout the CNS. Serotonin has multiple pharmacological actions in the body: Sleep – it controls the sleep-wake cycle, it increases slow wave sleep, accelerates sleep onset and increases the total sleep time. Serotonin has an influence on cognition, sensory perception, motor activity, temperature regulation, nociception, appetite,³ sexual behaviour and hormone secretion.

Table I: Serotonergic drugs – primary actions and clinical uses²

Receptor	Action	Drug examples	Clinical disorder
5-HT _{1A}	Partial agonist	Buspirone, ipsaperone	Anxiety, depression
5-HT _{1D}	Agonist	Sumatriptan	Migraine
5-HT _{2A/2C}	Antagonist	Methysergide, trazodone, risperidone, ketanserin	Migraine, depression, schizophrenia
5-HT ₃	Antagonist	Ondansetron	Chemotherapy-induced emesis
5-HT ₄	Agonist	Cisapride	Gastrointestinal disorders
5-HT transporter	Inhibitor	Fluoxetine, sertraline	Depression, obsessive-compulsive disorder, social phobia, posttraumatic stress disorder

It also modulates cognition, reward, learning and memory. A significant increase in serotonin serum levels can cause psychotic behaviour and can be hallucinogenic!

At least 14 5-HT receptor subtypes have been delineated by pharmacological analyses and cDNA cloning. The multiple 5-HT receptor subtypes cloned comprise the largest known neurotransmitter-receptor family. Experimental strategies for evaluating the role of 5-HT depend on techniques that manipulate tissue levels of 5-HT or block 5-HT receptors.

Some serotonergic drugs

- Desvenlafaxine (EXSIRA) is a serotonin-noradrenaline reuptake inhibitor (SNRI), blocking the reuptake of both monoamines. It has very little affinity for other postsynaptic receptor sites and is less likely to produce some of the side-effects associated with the tricyclic antidepressants. Desvenlafaxine is effective in the treatment of vasomotor symptoms in perimenopause.
- Duloxetine (YELATE) is also a SNRI that is widely used. It is well absorbed and has a half-life of 12 hours and is dosed once daily. It is indicated for major depressive disorders, peripheral neuropathic pain and for urinary stress incontinence in Europe. The normal dose is 60–120 mg daily.

Serotonin in aging

Serotonin is linked to many functions such as mood, aggression, feeding and sleep. Dysregulation of 5-HT function is believed to be involved in depression, impulsivity and suicide. Additionally, modulation of cholinergic neuronal activity by 5-HT may play a role in higher cognitive processes such as memory and learning. Alterations in serotonergic function may account for behavioural disturbances commonly observed in the elderly. Several postmortem human studies have reported a reduction in the number of cortical 5-HT 1A, 5-HT 1B/D and 5-HT 2A binding sites with age in the frontal lobe, occipital lobe and hippocampus. There is, however, scant literature on the effect of aging on the 5-HT transporter. Geriatric depression carries an increased risk of suicide, higher mortality, and the potential for future development of dementia.

Postmortem studies also demonstrated increased 5-HT 2A receptors in the pre-frontal cortex of suicide victims and depressed persons who died of natural causes, consistent with the hypothesis that 5-HT 2A receptors up-regulate in response to a defect in serotonergic neurotransmission. Similarly, animal and human studies suggest that therapeutic effect of electroconvulsive therapy (ECT) in depression is linked to enhanced neuronal responsiveness to 5-HT. The clinical effectiveness of selective 5-HT reuptake inhibitors (SSRIs) is believed to be mediated through enhancement of extracellular 5-HT.

There is considerable evidence in the postmortem literature supporting direct involvement of the 5-HT system in cognitive and behavioural symptomatology in Alzheimer's disease (AD). The 5-HT 2A receptor is associated with cholinergic nerve terminals in the cerebral cortex and hippocampus. It is also postulated that 5-HT may play an important role in age-related

memory impairment. Strosznajder et al. demonstrated aging to diminish the stimulatory effect of 5-HT on arachidonic acid uptake into membrane lipids, a mechanism believed to be important in memory processing.⁴ Serotonin most likely affects memory by modulation of other neurotransmitter systems, especially the cholinergic system, an effect potentially mediated by 5-HT 1A, 5-HT 2A and 5-HT 3A receptors. Serotonergic dysfunction appears to be closely linked to the behavioural aspects of AD. It also appears that greater 5-HT deficits have been observed in AD patients with depressive symptoms and aggression. Citalopram administered to AD patients resulted in significant improvement in emotional blunting, confusion, anxiety, fear, depression and motor restlessness.

Selective serotonin reuptake inhibitors in older age

Depression is common in older adults, affecting up to 9.3% of those over 75 years. The introduction of SSRIs replaced the first- and second-generation antidepressants. This is because it is a more rational treatment, based on specific mechanisms and is an effective treatment with fewer side-effects, particularly in the older patients who have a greater sensitivity to cardiovascular and CNS effects.

Efficacy of SSRIs

Some problems with SSRIs that occur in young patients, such as the emergence of suicidal thoughts and acts, are not observed in older patients. In contrast to their relatively fast onset of action in younger adults, SSRIs may take longer to work in older patients. In placebo-controlled trials, the SSRIs were effective in achieving a response in depressive symptoms in the elderly. Older men with a higher baseline severity and first episode of illness have higher response rates. There is some evidence for the use of SSRIs in elderly subjects with comorbid physical conditions.

Taylor et al. found that SSRIs showed a significant advantage over placebo for depression remission, response and in improving quality of life.⁵ Comparative studies versus tricyclic antidepressants (TCAs) showed that they are comparable in achieving remission of late life depression. Comparisons with other antidepressants show a paucity of evidence for a superior efficacy of SSRIs over other classes of antidepressants. They appear to be as effective in treating depression in the elderly as trazodone, tianeptine, moclobemide, venlafaxine, mirtazapine and bupropion.

Sertralene (DYNA SERTRALENE, SERTRA)

Sertralene is a selective serotonin reuptake inhibitor (SSRI). It is indicated for major depressive disorders, obsessive compulsive disorders and panic disorders. Sertralene has a bioavailability of 45%, a plasma half-life of 22–27 hours and is 98% protein bound. Its daily dose is 50–200 mg per day. It has a low risk of overdose and must not be used with MAO Inhibitors.

Citalopram (CILIFT)

Citalopram is one of the earlier SSRIs. It has a bioavailability of 80%, a half-life of 33–38 hours and is 80% protein bound. Indications: major depressive disorders, obsessive compulsive

disorders, panic disorders and social phobia. Side-effects include nausea, insomnia, sexual disorders, shakiness and sweating. It is contraindicated in patients treated with MAOI and in patients younger than 25 years of age due to a higher incidence of suicide in this group. Studies showed an 85% efficacy in the treatment of anxiety disorders.⁶

Escitalopram (CITRAZ, ZYTOMIL)

Escitalopram is the active *s*-isomer of citalopram. It has a bioavailability of 80%, a plasma half-life of 27–32 hours and is 80% protein bound. The daily dose is 10–30 mg. It is indicated for major depressive disorders and anxiety disorders which include general anxiety disorder, social anxiety disorder and obsessive-compulsive disorders. It is said to be marginally safer than citalopram with the same efficacy.

Safety of SSRIs

Various studies have shown that SSRIs are better tolerated in older people compared with the tricyclic antidepressant or serotonin-norepinephrine reuptake inhibitors (SNRIs).⁷ This is due to their side-effect profile and to less clinically significant drug interactions with other compounds. The most reported side-effects of SSRIs are nausea, dry mouth, constipation, diarrhoea, anorexia, drowsiness, dizziness, lethargy, sleep disturbance, tremor and anxiety. Hyponatraemia is the most common electrolyte disturbance, especially with fluoxetine. The rest of the side-effects have a low incidence, but can be serious, like the serotonin syndrome which is more likely with TCA treatment. SSRIs have a little known but potentially disastrous interaction with tamoxifen, the Selective Estrogen Receptor Modulator (SERM) used in the treatment of oestrogen-receptor positive breast cancer.⁸

Creating a feeling of well being?

It is obvious that serotonin plays a significant role in the emotional wellbeing of people – whether they are young or old! How much does it contribute to happiness and creativity in the life of people? Can't we just buy serotonin tablets, take them every day and be happy? Unfortunately, serotonin taken orally will be destroyed in the gastrointestinal tract and can not reach the bloodstream and brain.

Eating foods that contain the essential amino acid known as tryptophan can help the body to produce more serotonin. In the body serotonin is formed through the metabolism of tryptophan, which is a serotonin precursor in the body.

Is there a way of increasing serotonin in the body without drugs?

There has been a lot written and research done on ways to increase serotonin in the body. The following four suggestions have been best researched:

1. Alterations in thought – self-induced changes in mood can influence the synthesis of serotonin in the body.
2. Exposure to bright light – more than 3000 lux.
3. Exercise – the most consistent effect is seen when regular exercisers undertake aerobic exercises at a level with which they are familiar.
4. Diet – the ingestion of food containing tryptophan.⁹

The following foods naturally boost serotonin availability in the body: salmon, poultry, eggs, spinach, seeds, milk, soy products and nuts. These foods contain tryptophan in adequate quantities to increase serotonin in the body.

Conclusion

The SSRIs are an interesting group of medications that improve the treatment of depressive disorders significantly with a far more acceptable side-effect profile, providing a better quality of life for many patients, especially those who are older and frail.

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