The neurobiology of depression—revisiting the serotonin hypothesis. II. Genetic, epigenetic and clinical studies†

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The serotonin system originates from a small number of neurons (a few hundred thousand of the 100 billion in man) located in the midbrain raphe nuclei, that project widely throughout the central nervous system to influence a large array of inter-related biological functions, not least of which are circuits involved in mood and emotion. The serotonin hypothesis of depression has postulated that a reduction in serotonin leads to increased predisposition to depression. Indeed, it has become evident from therapeutic strategies that affect serotonin activity, that alterations in serotonin may not only predispose to depression, but also to aggressive behaviour, impulsivity, obsessive–compulsive behaviour and suicide. Many potential mechanisms known to alter the genes that regulate the serotonin system, including developmental epigenetic modifications, are presented, as additional evidence implicating the serotonin system. This second issue of two special issues of Philosophical Transactions B presents a series of reviews, perspectives and new findings that argue that the serotonin hypothesis remains an important idea that continues to guide research into the aetiology and treatment of depression.

1. Laurent Descarries

The impetus for assembling these volumes was the 33rd International Symposium of the Groupe de Recherche sur le Système Nerveux Central entitled ‘The neurobiology of depression—revisiting the 5-HT hypothesis’ held at the Université de Montréal, and organized by Laurent Descarries, Paul Albert and Chawki Benkelfat. During the assembly of this volume, we learned of the untimely passing of Laurent Descarries, the organizer and driving force behind the meeting. Apart from his passion for bringing together current researchers with interest in serotonin for a renewed focus on the amazing variety of actions of this pervasive neurotransmitter, Laurent was a guiding light to a generation of outstanding researchers in neuroscience. More than any other Canadian researcher, he has drawn attention to the detailed anatomy and function of the serotonin system, and its implication of brain disorders. With Alain Beaudet, he was the first to quantify serotonergic innervation to the frontal cortex using labelling with [3H]5-HT [1,2]. His recent findings using electron microscopy and positron emission tomography (PET) neuroimaging to investigate antidepressant-induced trafficking of 5-HT1A receptors and serotonin transporters is reviewed in his contribution to Volume I [3]. Another important contribution that he was strongly involved with was the identification of cotransmission of glutamate with monoamines, including dopamine and serotonin [4]. He had numerous publications addressing the localization, dynamics and function of other neurotransmitters and their receptors, but his primary focus was on the serotonin system and its involvement in depression and antidepressant action. As reflected in these two volumes, he was committed to bridging the worlds of basic and clinical research. This was also exemplified by his research, for example, to examine 5-HT1A receptor dynamics not only...

†This issue is dedicated to the memory of Laurent Descarries.
at the ultrastructural level, but also in the whole animal, using PET [5]. He has collaborated with many and will be greatly missed.

2. Genetics, epigenetics and depression

While Volume I was focused on cellular and molecular changes in the serotonin system in animal models of depression, Volume II focuses on alterations in the serotonin system in human depression and related disorders. Genetic transmission is a recognized factor in depression and heritability runs at about 40 per cent for major depression [6]. The studies presented by Talati and co-workers [7] reminds the reader that the risk for depression can be transmitted over generations, and a major part of this transmission is due to genetic transmission from parents to offspring. The family cohorts collected by this group offer perhaps the strongest genetically related group with potentially greater homogeneity for identifying significant linkage between specific genetic loci and depression using high-throughput genome sequence analysis. In particular, they find that the short allele of polymorphism of the 5-HT (5-hydroxytryptamine or serotonin) transporter is enriched in at-risk offspring, even though an association with depression per se was not detected. They also report evidence of structure changes (thinning of the cortical mantle), as well as reduced activity of the right parieto-temporal cortex in the high-risk group. The identification of the DNA methylene of these subjects was thought to help identify epigenetic loci that are linked to environmental risk for depression. For example, early life abuse of children has been associated with increased lifelong methylation of specific loci, such as the glucocorticoid receptor promoter, that leads to altered baseline transcription and confer increased risk for depression and suicide [8]. Booij et al. [9] review evidence that alterations in the DNA methylation of gene regulatory regions in several key genes in the serotonin system and the stress axis, associated with early life stress, are risk factors for depression and related illnesses. DNA methylation is the most stable epigenetic modification, and early life changes in DNA methylation can persist into adulthood and confer lifetime risk for depression. Their studies are suggesting that in some genes, DNA methylation alterations observed in brain may be paralleled by similar changes in peripheral tissues, and thus sample peripheral tissues such as blood, may provide a quantifiable marker for stress loading due to childhood abuse. Mann [10] reviews biochemical, genetic and imaging evidence that alterations in serotonin neurotransmission to specific forebrain regions, such as anterior cingulate or ventral medial prefrontal cortex is associated not only with suicide, but also with suicidal intent. A reduction in 5-HIAA (5-hydroxyindoleacetic acid) is observed in suicide as seen in aggression phenotypes. In particular, decreased activity of anterior cingulate and prefrontal cortical regions is correlated with lethality of suicide attempt. As for depression, there appears to be a strong effect of early life stress in predisposing to suicidal behaviour.

Genetic analysis of homogeneous populations has been crucial for the identification of a rare but functional stop codon HTR2B variant as a risk factor for impulsive-aggressive behaviour. The heritability of a measure of impulsive behaviour in twin studies is between 30 and 50 per cent particularly in males, and increasing with age from 12 to 14 years [11]. Several genes in the serotonin system have been associated with impulsivity, and this has been supported by the aggressive phenotype of knockout mice for several of these candidate genes. Bevilacqua and Goldman [12] characterized a genetically homogeneous Finnish male population’s violent and impulsive-aggressive behaviour using deep sequence analysis. This population was characterized previously with reduced 5-HT metabolite 5-HIAA, a biological finding and hallmark associated with hetero- and auto-aggressive behaviour. The stop codon mutant that they identified results in a non-functional 5-HT2B variant; on the basis of this observation, they also reported that mice lacking 5-HT2B receptors display impulsive behaviour. While this mutation appears only in the Finnish population, it provides mechanistic insight that other common genetic variants of the 5-HT2B receptor could associate with impulsive behaviour and that therapeutic strategies targeting 5-HT2B receptors hold promise as alternative treatments of impulsivity.

Murphy et al. [13] focus on an affective/anxiety disorder related to serotonin regulation, namely obsessive-compulsive disorder (OCD). OCD is frequently comorbid with depression (70%), and like depression is associated with long/short promoter polymorphism in the serotonin transporter gene (SERT). However, while the low activity SERT alleles are associated with depression, greater SERT activity alleles associate with OCD. Similarly, there is some evidence that transgenic overexpression of SERT leads to ‘obessive’ behaviour in mice. In addition to serotonin-related genes, there is clear evidence of associations with glutamatergic genes, and more recent treatments for OCD are targeting the glutamate system. In addition, genetic association and transgenic mouse models suggest involvement of neuronal synaptic genes and developmental alterations in this disorder. Thus, like depression, there is increased evidence for multiple targets, consistent with the disorder’s well-described known aetiological and clinical heterogeneity. Here, as in the case of other related disorders, including the disorders of mood regulation, alterations of serotonin neurotransmission remain central and could not be overlooked.

3. Neuroimaging in depression

The hypothesis that genetic or early life events may gradually mould circuit alterations that can be detected by PET or functional magnetic resonance imaging (fMRI) has been examined. Studies in post-mortem tissues from depressed subjects indicate a reduction in cortical grey matter, and reduced glial cellularity are observed in prefrontal cortex and hippocampus of depressed subjects [14]. Fisher & Hariri [15] have focused on amygdala reactivity to fearful or threatening faces or images, as detected by multi-modal PET and blood-oxygen-level-dependent (BOLD)-fMRI. Increased 5-HT1A autoreceptor levels inversely correlated with amygdala reactivity to threat, consistent with increase in 5-HT autoinhibition reducing fear responsiveness. Furthermore, it was found that the C (−1019) G polymorphism that associates with increase in 5-HT1A autoreceptor levels [16], was also associated with reduced amygdala reactivity to threatening stimuli [17]. Thus, the combination of PET, BOLD-fMRI and genetic studies has the potential to link transcriptional changes to altered gene expression and ultimately to behavioural responses that associate with anxiety or depression.
Hesselgrave & Parsey [16] and their group have performed extensive studies of alterations in 5-HT1A receptor binding detected by PET imaging in depressed subjects. Their findings show that depression is associated with increase in 5-HT1A receptor levels, most prominently in the raphe nuclei. This increase is even greater in remitted patients than in patients with current depression having been recently medicated or control subjects. This suggests that increase in 5-HT1A autoreceptor binding may represent an intrinsic predisposing factor to depression. Consistent with this, they found that increased 5-HT1A autoreceptor expression was associated with the C (–1019) G polymorphism of the 5-HT1A gene that leads to upregulation of the 5-HT1A autoreceptor and is associated with depression [18]. These studies provide clinical evidence that genetic alterations that lead to transcriptional dysregulation of key serotonin-regulatory genes such as of the 5-HT1A receptor can be associated with a predisposition to depression. They propose future studies using novel 5-HT1A agonist tracers that will detect functional 5-HT1A receptors and provide a more refined identification of functional changes in depression.

4. Antidepressant therapy
The most widely used antidepressant treatments are serotonin-specific uptake inhibitors that selectively target the serotonin system. However, only 50 per cent of patients respond to these drugs and effective remission occurs less than 30 per cent of the time [19], hence new antidepressant strategies are needed. Blier & El Mansari [20] present the concept that brain monoamine systems are intimately interconnected, and that for effective antidepressant therapy it is important to consider a coordinated regulation of the three major monoaminergic systems together: serotonin, dopamine and noradrenaline. It is proposed that while selective serotonin reuptake inhibitor (SSRI)-induced enhancement of serotonin neurotransmission at forebrain targets may be important for treatment response, inhibitory actions of 5-HT at dopaminergic and noradrenergic neurons may limit the response and lead to adverse actions, such as sexual dysfunction or lack of energy, that prevent remission. Drug combinations or compounds that combine appropriate pharmacology to prevent 5-HT-induced inhibition of monoaminergic systems is therefore proposed, as a means to improve tolerance, and hence the overall effectiveness of chronic SSRI treatments.

Young [21] has reviewed the use of acute tryptophan depletion (ATD) in human subjects as an approach to reduce serotonin levels, using it to interrogate the role of serotonin in depression or depressive behaviours. Importantly, the mood lowering effect of ATD is most evident in subjects who have had clinical depression, eliciting a relapse of depressive symptoms, at the time of ATD, concurrently. On the other hand, tryptophan supplementation appears to improve mood by improving social interaction (agreeableness). It is emphasized that, while serotonin is a critical regulator of processes that can determine mood, its action is complemented by psychosocial factors and lifetime experience that potentiate its actions.

The importance of psychosocial environment in combination with serotonin is also postulated to enhance the response to SSRI treatment [21]. An important problem with most current antidepressant treatments including SSRI treatment is that several weeks of treatment are required before clinical improvement is observed. Harmer & Cowen [22] propose a neuropsychological framework to explain this delay, suggesting that it represents the time for the emergence of a conscious positive bias in emotional processing. They argue that the progressive awareness of the positive effects of SSRI treatment on the emotional balance is central to the antidepressant effect. This time period is consistent with SSRI-induced changes in neurogenesis and synaptic plasticity, as well as a greater desensitization of 5-HT1A auto-receptors. As a result, it is proposed that early improvements in emotional bias signal effectiveness and could connote treatment response.

5. Conclusion
Taken together, these articles indicate the central relevance of the serotonin system(s) to the investigations of the pathophysiology of mood disorders in addition to the understanding of many associated behavioural phenotypes, such as stress sensitivity, emotionality, impulsivity, compulsivity or suicidal behaviour. The technological advances in neuroimaging, high-throughput sequence analysis and a better characterization of endophenotypes and behavioural traits, as well as the increasing use of homogeneous populations, all are believed to lead the way towards novel quantifiable biological markers for depression and response to antidepressant therapies. By uncovering new potential therapeutic targets, these approaches should provide impetus for earlier and more effective interventions by both pharmacological and psychosocial treatment strategies.

References


