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Introduction

The neurobiology of depression—revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms

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The serotonin (5-HT) hypothesis of depression dates from the 1960s. It originally postulated that a deficit in brain serotonin, corrected by antidepressant drugs, was the origin of the illness. Nowadays, it is generally accepted that recurring mood disorders are brain diseases resulting from the combination, to various degrees, of genetic and other biological as well as environmental factors, evolving through the lifespan. All areas of neuroscience, from genes to behaviour, molecules to mind, and experimental to clinical, are actively engaged in attempts at elucidating the pathophysiology of depression and the mechanisms underlying the efficacy of antidepressant treatments. This first of two special issues of *Philosophical Transactions B* seeks to provide an overview of current developments in the field, with an emphasis on cellular and molecular mechanisms, and how their unravelling opens new perspectives for future research.

Keywords: depression; serotonin; neurobiology

1. THE VENUE

In May 2011, a 2-day conference entitled 'The neurobiology of depression—revisiting the 5-HT hypothesis' was held at the Université de Montréal. This was the 33rd International Symposium of the Groupe de Recherche sur le Système Nerveux Central that annually gathers leading researchers across the world to discuss a particular topic of neuroscience. As defined by its organizers from three Canadian universities, Laurent Descarries (Université de Montréal), Chawki Benkelfat (McGill University) and Paul R. Albert (University of Ottawa), the purpose of this particular meeting was to bring together experts from different disciplines to review current knowledge on the neurobiology of depression, including their most recent results. The event was sponsored by the three universities, the Canadian Institutes for Health Research, the Réseau Québecois de Recherche sur le Suicide (FRSQ), the Savoy Foundation and Eli Lilly Canada. The 20 lectures at the meeting were the basis for the present publication of two special issues of *Phil. Trans. R. Soc. B.*

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One contribution of 11 to a Theme Issue 'The neurobiology of depression—revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms'.

2. THE DISEASE

Depression, that is major depressive disorder (MDD), is a calamity for individuals and society. If we have not experienced it ourselves, we all know someone who has been struck by this disease. Twenty per cent of women and 15 per cent of men suffer at least one episode in their lifetime. In the USA, the lifetime prevalence in the general population is estimated at 16.2 per cent [1].

MDD is characterized by two or more weeks of depressed mood or diminished interest, associated with symptoms such as disturbed sleep, decrease in appetite and libido, psychomotor changes, reduced concentration, excessive guilt and suicidal thoughts or attempts [2]. It is insidious and often recurrent. Although depressive episodes can be treated well with antidepressant medication, structured forms of psychotherapy or a combination of these, the rate of recurrence is high [3], with each episode raising the probability of a new one by 16 per cent [4]. MDD is the second leading cause of disability worldwide, in the age category of 15–44 years for both sexes combined, surpassed only by ischaemic heart disease [5]. It is expected to be first in high-income countries in 2030 [6]. The cost for society is billions of dollars per year.

3. THE 5-HYDROXYTRYPTAMINE HYPOTHESIS

Depression has too long been considered as an illness of the soul. Currently, it is viewed as a disorder of the brain. This shift in paradigm began more than 50 years ago, soon after the biogenic amines, notably noradrenaline and serotonin (5-hydroxytryptamine, 5-HT), were discovered as brain transmitters. The monoamine hypothesis of depression was proposed by Schildkraut [7], referring essentially to catecholamines. Then, Coppen [8] emphasized the possible role of 5-HT. In its original formulation, the 5-HT hypothesis postulated a deficit in 5-HT as a primary cause, reversed by antidepressants, which would restore normal function in depressed patients. Indeed, a variety of functional deficits of 5-HT neurotransmission in brain circuits known to regulate emotions, whether primary or secondary, have consistently been associated with aspects of the pathophysiology of MDD, as suggested by post-mortem and genetic, neurochemical, neuroimaging and pharmacological studies [9]. More recently, reports that high-risk relatives of MDD patients are more sensitive to 5-HT challenge procedures, such as depletion of tryptophan/5-HT [10,11], and evidence that altered serotonergic function is still present in MDD patients in remission [12], suggest that altered or low 5-HT may represent a risk factor and trait diathesis increasing vulnerability to MDD [13].

The modelling of a mental disorder exclusively based on the dysregulation of a particular neurotransmitter system is obviously simplistic and open to criticism. Yet, it has provided an impetus for much of the subsequent research. Over the years, the 5-HT hypothesis of depression has been refined, to take into account new knowledge and several apparent inconsistencies, including: that a transient lowering of central nervous system 5-HT achieved experimentally in healthy controls devoid of risk for mood disorders has only modest effects on mood, if any; that not all patients benefit from drugs enhancing serotonergic neurotransmission [14]; and that several drugs apparently devoid of major effects on serotonergic neurotransmission are effective to improve mood [15].

4. CURRENT TRENDS

Today, it is generally accepted that a variety of genetic, environmental and neurobiological factors are implicated in depression. All areas of neuroscience, from molecules to mind, genes to behaviour, and laboratory to bedside, are actively engaged in attempts at elucidating the pathophysiology of depression as well as the mechanisms underlying the efficacy of antidepressant treatments. In most of these fields, the 5-HT system remains at the core of recent advances. 5-HT is considered to be crucial for the development of the human and mammalian brain [16]. An emerging body of experimental evidence provides an insight into how dysfunctions of serotonergic tone early in life, whether increased or decreased, can modulate brain pathways development, differentiation and maturation, as well as affect sensitivity to aversive stressors and, more generally, emotion regulation in adults. Through a cascade of intracellular mechanisms, the formation, function and survival of 5-HT neurons is now known to depend on trophic factors, including the brain-derived neurotrophic factor, a neuronal protein produced and released in an activity-dependent manner [17]. Animal and human studies targeting the 5-HT plasma membrane transporter, SERT, illustrate how methods and concepts have shifted in emphasis: SERT knockout mice, whether through genetic deletion or transient pharmacological ablation in early life [18], demonstrate an increased serotonergic tone and various subtle neurodevelopmental alterations reflecting 5-HT properties as a potent trophic factor early in life, and express a depressive- and anxiety-related behavioural phenotype as adults. In humans, carriers of the *s* allele of SERT, a genetic variant that reduces the expression of SERT, are more sensitive to stress-induced activation of amygdala [19], less sensitive to the cingulate–amygdala coupling at play during fear extinction [20] and more prone to anxiety-like temperaments [21] and to depressive recurrence in the context of environmental adversity [22].

5. RECENT ADVANCES

The heuristic value of a hypothesis often measures itself against the richness, originality and quality of the data it helps to generate. In this sense, the 5-HT hypothesis of depression resists the passage of time considering the wealth of information it continues to generate. This is particularly well illustrated by the articles assembled in this first special issue, subtitled 'Cellular and molecular mechanisms'.

The first article, by Gaspar & Lillesaar [23], is a broad and up-to-date account of previous and novel data demonstrating diversity in the morphological and functional organization of the brain 5-HT system. These authors recently studied the genetic programming of this system in mice and zebrafish. In both species, 5-HT neurons differ in the transcription factors contributing to their acquisition of a 5-HT identity. For example, there are PET1-dependent and PET1-independent 5-HT neurons in the midbrain raphe of mice, displaying distinct anatomical features. In zebrafish, all raphe neurons express *pet1*, but Pet1-independent 5-HT cell groups are found in the forebrain. These observations support the view of a number of distinct 5-HT subsystems with unique genetic programming and functions.

In the next article, Tanaka *et al.* [24], using *in situ* hybridization describe the distribution of the mRNA for all 5-HT receptor (Htr) subtypes in mouse hippocampus, excluding Htr6. At the cellular level, their results support the view that several Htr subtypes may be expressed by the same neurons. At the regional level, they report changes in the expression pattern for Htr1a, Htr2a, Htr2c and Htr7 expression along the dorsal–ventral axis of hippocampus. Given the proposed functional differentiation of hippocampus along its long axis, with its dorsal region more involved in cognitive functions and its ventral blade in mood and anxiety, they suggest that 5-HT receptors enriched in the ventral segment, such as Htr1a, Htr2c and Htr7, likely play a role in mood- and anxiety-related behaviour, as well as in the anxiolytic and antidepressant effects of selective 5-HT reuptake inhibitors (SSRIs).

The review of Albert [25] is a thorough update on recent discoveries in 5-HT_{1A} gene regulation, and its link with psychiatric disorders. It provides a strong argument that dysregulation of 5-HT_{1A} autoreceptor and heteroceptor (genetic or environmental in basis,

or both) is a risk factor for depression and anxiety. Although the findings in the literature are not all consistent (animal data are much clearer than the human data), overall the data suggest that upregulation of 5-HT_{1A} autoreceptors and consequent reduction in serotonergic tone may be a risk factor for depression.

In their article, Descarries & Riad [26] summarize their immuno-electron microscopic studies on the trafficking of the 5-HT_{1A} autoreceptor in rats acutely or chronically treated with the prototypic SSRI, fluoxetine (Prozac). These studies have led to the brain imaging demonstration of an internalization of this receptor in the dorsal raphe nucleus of human volunteers administered a single oral dose of Prozac. Preliminary immuno-electron microscopic results are also reported, indicating that upon chronic, but not acute treatment with fluoxetine, the plasma membrane 5-HT transporter, SERT, internalizes and is degraded in both the cell bodies and axon terminals of midbrain 5-HT neurons.

The paper by Lesch *et al.* [27] analyses the effects of *Tph2* gene deletion or inactivation in mice on emotional and aggressive behaviour, and their morphological, neurochemical and functional correlates, in comparison with other genetic mouse models. It provides important insights into the relationship between specific behavioural phenotypes and neurobiological parameters. As several assumed relationships, e.g. between anxiety and depression and 5-HT_{1A} autoreceptor function in depression, do not hold true in this particular model, it is concluded that approaches focusing on TPH2 variants in humans may reveal unexpected aspects of the role of 5-HT in brain development and in disorders characterized by negative emotionality, aggression and antisocial behaviour.

After recapitulating the history of 5-HT implication in depression, with particular emphasis on 5-HT deficiency, the article of Jacobsen *et al.* [28] presents new evidence that 5-HT biomarker abnormalities associated with depression occur consequent to severely reduced brain levels of extracellular 5-HT in a mouse model of naturalistic 5-HT deficiency, the tryptophan hydroxylase 2 His439 (Tph2KI) knockin mouse. Other studies examining the functional consequences of depression-related TPH2 variants are also reviewed, as growing evidence for an association of functional coding and non-coding polymorphisms in *Tph2* with depression and other psychiatric diseases.

Latapy *et al.* [29] provide the first description of the behavioural phenotype of mice with a CAMKCRE-mediated knockout of the kinase GSK3β in forebrain pyramidal neurons. These mice show an exaggerated response to amphetamine, reduced anxiety and greater social interactions, but no change in spontaneous locomotion or abnormality in the tail suspension test or the forced swim tests, nor in aversion response to social defeat. In contrast, GSK3β heterozygotes show no change in social interactions and a positive effect on social defeat. Thus, the modulation of behaviour by GSK3 kinases appears dependent on their anatomical location, and hence their specific contribution to the effects of psychiatric drugs.

In contrast to the previous articles on serotonergic mechanisms, the paper by Duman & Li [30] discusses the role in depression of neuronal atrophy owing to stress or reduced growth factor support, and focuses on their studies of the mechanisms underlying the rapid actions of glutamatergic NMDA receptor antagonist, ketamine. Acute treatment with ketamine leads to rapid synaptogenesis and spine formation in the prefrontal cortex via a signalling pathway involving mTOR activation, and can reverse dendrite atrophy induced by chronic stress. These actions correlate with the rapid effects of ketamine on anxiety and depression-like behaviours, and suggest that modulation of the glutamate system at specific sites may provide a new approach to treat depression.

The article by Massart *et al.* [31] also considers alternatives to the monoamine theory of depression. After an overview of current hypotheses mostly centred on dysfunctions of the hypothalamic–pituitary adrenal axis, circadian rhythms and neuroimmune processes, including a role for epigenetics in depression, it analyses various changes in the expression of genes controlling the activity of the hypothalamic-pituitary-adrenal axis and those involved in epigenetic regulations, which were recently detected in the glucocorticoid receptor-impaired mouse model of depressive disorders.

The last paper of this issue, by Hellström *et al.* [32], focuses on a model of the role of early life environment in determining adult life stress responsiveness. Maternal licking and grooming of the pups leads to increased levels of hippocampal glucocorticoid receptors via altered epigenetic modifications, including DNA methylation of the hippocampal-specific promoter, increasing negative feedback regulation and reducing stress responsiveness throughout life. This study probes the neurohormonal basis by which licking and grooming or tactile stimulation triggers this pathway and regulates gene expression. These studies implicate both 5-HT and thyroid hormone in early life modifications of hippocampal gene expression by activation of a specific transcription factor, NGFA, and have important implications for the role of early epigenetic and transcriptional modifications in gene–environment interactions.

6. SEROTONIN AND BEYOND

Taken together, these papers illustrate the multi-faceted developmental and signalling actions of 5-HT in regulating behaviours that model depression and anxiety. Animal models as described earlier have shown that modifying any of the components of the 5-HT system, including tryptophan hydroxylase, 5-HT transporter, specific 5-HT receptors (5-HT_{1A}) or their regulation (e.g. by Deaf1) or downstream signals (e.g. GSK3β), or transcription factors that regulate the 5-HT phenotype (e.g. PET1), all lead to alterations that mimic the depressed state in humans. In some cases, early life alterations in 5-HT can also lead to lifelong behavioural changes that mimic depression or anxiety. Additional mechanisms involving other systems, such as glutamate-driven alterations in synaptic connectivity or alterations in growth factor support, can also impact on the development and treatment of the depression phenotype.

By assembling these contributions as a special issue of *Phil. Trans. R. Soc. B*, we have endeavoured to illustrate how the diverse aspects of a disease, first described and investigated in patients, may be taken to the wet

laboratory, to dissect its causes and mechanisms in simpler model organisms. Results from these studies provide new viewpoints on the disease itself and, sometimes, novel approaches for its diagnosis and its treatment, as well as for future research.

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