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The Neurobiology of Depression: an Integrated Overview from Biological Theories to Clinical Evidence

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Abstract Depressive disorders are heterogeneous diseases, and the complexity of symptoms has led to the formulation of several aethiopathological hypotheses. This heterogeneity may account for the following open issues about antidepressant therapy: (i) antidepressants show a time lag between pharmacological effects, within hours from acute drug administration, and therapeutic effects, within two-four weeks of subchronic treatment; (ii) this latency interval is critical for the patient because of the possible further mood worsening that may result in suicide attempts for the seemingly ineffective therapy and for the apparent adverse effects; (iii) and only 60–70 % of treated patients successfully respond to therapy. In this review, the complexity of the biological theories that try to explain the molecular mechanisms of these diseases is considered, encompassing (i) the classic "monoaminergic hypothesis" alongside the updated hypothesis according to which long-term therapeutical action of antidepressants is mediated by intracellular signal transduction pathways and (ii) the hypothalamic–pituitary-adrenal axis involvement. Although these models have guided research efforts in the field for decades, they have not generated a compelling and conclusive model either for depression pathophysiology or for antidepressant drugs' action. So, other emerging theories are discussed: (iii) the alterations of neuroplasticity and neurotrophins in selective vulnerable cerebral areas; (iv) the involvement of inflammatory processes; (v) and the alterations in mitochondrial function and neuronal bioenergetics. The focus is put on the molecular and theoretical links between all these hypotheses, which are not mutually exclusive but otherwise tightly correlated, giving an integrated and comprehensive overview of the neurobiology of depressive disorders.

Keywords Depressive disorders · Aethiopathological hypotheses · Antidepressant therapy · Molecular pharmacology · Neuroimaging · Mitochondrial bioenergetics

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Biological Theories and Molecular Mechanisms of Depression Pathogenesis

Major depressive disorder (MDD) is thought to result from the dysfunction of many neurotransmitter or metabolic systems. Both basic and clinical studies have proven that noradrenaline (NA) and 5-hydroxytriptamine (5-HT) neurotransmitter systems are involved in depression. This classic "monoaminergic hypothesis" of depression will be firstly discussed, encompassing the updated hypothesis according to which long-term therapeutical actions of antidepressants are mediated by post-receptor intracellular targets, i.e. by adaptations in neuronal function to specific signal transduction pathways. The hypothalamic–pituitary–adrenal (HPA) axis involvement in MDD will also be considered, since hyperactivity of HPA axis is another strong biological correlate of depression.

Although these models have guided research efforts in the field for decades, they have not generated a compelling and conclusive model either for the pathophysiology of depression or for antidepressant drugs' action, also considering that one third of patients are non-responsive to the current antidepressant pharmacotherapy.

So, other emerging theories (not to be considered mutually exclusive) will be discussed, highlighting the complex links with the previous mentioned hypotheses, i.e. (i) the alterations of neuroplasticity and neurotrophins in selective vulnerable

cerebral areas and (ii) the involvement of inflammatory processes.

The Monoaminergic Hypothesis of Depression

Brain neurochemistry was one of the first examined aspects in the study of the biological basis of depression. The original monoamine hypothesis is derived from the "pharmacocentric" clinical finding that monoamine depletion by the antihypertensive drug reserpine caused depression in patients not suffering of the disease before reserpine therapy. This hypothesis was supported by the discovery that prototypical antidepressants [the tricyclics (TCA) and monoamine oxidase inhibitors (MAOi)] cause the short-term increase of monoamine synaptic concentrations. Subsequent findings reported the reduced concentrations of monoamine break down products in the cerebrospinal fluid (CSF), leading to the theory that not only a deficiency of NA and 5-HT but also of dopamine (DA) or of all three molecules together may occur in monoaminergic synapses [1].

However, the studies of NA and 5-HT metabolites in plasma, urine and CSF, as well as post-mortem studies on the brains of depressed patients, have yet to definitively identify this deficiency, even if the monoamine hypothesis continues to encourage researches. For example, the discovery of the neuronal-specific isoform (and not brain-specific) of the enzyme tryptophan hydroxylase TPH-2 by Zhang et al. [2] could explain why previous post-mortem studies on total enzyme activity did not show differences in tryptophan hydroxylase activity between patients with depression and controls, i.e. this is the reason why measurements of total tryptophan hydroxylase (TPH) activity in the central nervous system (CNS) are not informative. In fact, TPH catalyzes the rate-limiting step in 5-HT synthesis. Two isoforms of the TPH enzyme exist, encoded by TPH1 and TPH2 genes in humans and tph1 and tph2 genes in other mammals. TPH1 is expressed primarily in the periphery but is also present in CNS, whereas TPH2 is expressed exclusively in the CNS [3].

Positron emission tomographic (PET) study, using a ligand for brain monoamine oxidase (harmine labelled with ^{11}C), showed a 30 % increase of the enzyme content in a subgroup of depressed patients [4]. A neurochemical study measuring differences of monoamine metabolite concentrations between the internal jugular vein and the brachial artery showed lower NA metabolites production by the brain of patients than of controls [5].

The role of monoamines in depression has been further examined with the use of NA and 5-HT depletion paradigms in normal and drug-remitted individuals with depression by Miller and collaborators [6]. The results of this study demonstrated that, although the depletion of NA and 5-HT did not lead to depressive symptoms in normal individuals, patients who experienced remission after treatments were vulnerable to relapse on depletion of these monoamines. Similar results were shown by Ruhé et al. [7] in the meta-analysis reporting that monoamine depletion was correlated with decreased mood both in family history of MDD and in drug-free patients in remission. All these data indicate that NA and 5-HT are somehow involved in the maintenance of the antidepressant response but cannot alone explain either the pathophysiology of depression or the mechanism of action of antidepressants. This conclusion is also supported by the time required for the therapeutical action of antidepressant treatments to be evoked (several weeks), even though levels of monoamines are increased rapidly (within minutes) by these treatments.

The original monoaminergic hypothesis has been revised to include changes in downregulation and desensitisation of pre- and post-synaptic NA and 5-HT receptors: the continuing activation of these receptors during therapy would lead to adaptations in number and responsiveness of receptors, respectively, contributing to the delayed therapeutical action of antidepressants. Indeed, long-term antidepressant treatments were shown to downregulate the density of receptor sites for NA and 5-HT in early studies. The best characterised example is that long-term, but not short-term, administration of many types of antidepressants decreases the levels of β-adrenergic receptor (βAR) ligand-binding sites not only in some limbic brain regions, such as the hippocampus, but also in the cerebral cortex [8]. The ability of βARs to stimulate the formation of cyclic adenosine monophosphate (cAMP) is similarly decreased in these regions by long-term antidepressant treatments [9].

The α_2-noradrenergic receptors, which are usually pre-synaptic, modulate NA release by feedback inhibition: heightened receptor sensitivity has been described in patients with depression [10], which is consistent with reduced NA release.

A 5-HT_{1A} receptor sensitivity hypothesis has also been put forth by Blier and de Montigny [11]. This hypothesis states that long-term antidepressant treatments increase the function of post-synaptic 5-HT_{1A} receptors in the hippocampus. Depending on the type of treatment, they propose that this could occur by either the increased sensitivity of post-synaptic 5-HT_{1A} receptors or the desensitisation of 5-HT auto-receptors. One problem with this hypothesis is that the direct-acting 5-HT_{1A} receptor agonists are not clearly effective antidepressants, and increased 5-HT_{1A} neurotransmission is likely necessary but insufficient for antidepressant efficacy [9]. Moreover, these receptors can now be evaluated in patients by injecting specific agonists and measuring specific neuroendocrine responses, such as elevation of prolactin level [12], or by PET [13]: these results suggest that the sensitivity of these receptors is reduced in patients with depression.

The pre-synaptic 5-HT_{1B} receptors regulate the release of 5-HT by feedback inhibition. Post-mortem studies show that the levels of p11, a protein that improves the efficiency of 5-HT_{1B} signalling, are decreased in the brains of depressed patients [14].

As far as 5-HT receptor subtypes, a special mention would be made for the involvement of 5-HT_{2A} receptors in light of the recent evidence that hallucinogens as psylocibin, a 5-HT receptor agonist, cause antidepressant effects in human patients diagnosed with unipolar treatment-resistant depression [15]. The results show that the magnitude and persistence of the antidepressant effects are in line with previously observed effects of psilocybin in chronic psychiatric conditions.

Overall, it can be argued that the observed receptorial downregulations/desensitisations are indicative of sustained receptor activation secondary to continued elevations in monoamine levels after long-term antidepressant treatments [16]. Indeed, the tissue content of these receptors is decreased, but not completely eliminated, raising the possibility that sufficient number of receptors could remain to respond to the elevated levels of NA and 5-HT. Therefore, long-term antidepressant treatments may produce the sustained activation of the intracellular signal transduction cascades, and such intracellular factors may represent potential common targets for many different types of antidepressant treatments [17].

Nevertheless, studies on the phosphatidylinositol (PI) and cAMP second messenger systems have demonstrated a great heterogeneity of molecular alterations with respect to the considered type of depressive disorders. In fact, in MDD (i), $G\alpha_i$ (the inhibitory G protein α subunit) was increased, (ii) $G\alpha_s$ (the stimulatory G protein α subunit) remained unchanged and (iii) adenylyl cyclase (AC) activity was decreased in various cortical areas, suggesting an imbalance in favour of inhibitory functions over the stimulatory ones [17–19]. Also reduced inositol levels have been found in post-mortem brains of persons who have died by suicide [20] and in magnetic resonance spectroscopic (MRS) studies on the frontal cortex of depressed patients [21]. On the other hand, conflicting results were obtained in untreated versus treated MDD patients: the concentration of the transcription factor cAMP response element-binding protein (CREB) in the cortex was higher [22], but cAMP binding was lower [23], in treated patients than untreated. Moreover, Lowther et al. [23] showed that the behaviour of rats overexpressing CREB in the *dentate gyrus* correlated with that of rats treated with antidepressants, but the opposite occurred if CREB was overexpressed in the *nucleus accumbens* [24]. Interestingly, CREB upregulates the expression of the brain-derived neurotrophic factor (BDNF), that could be involved in the pathophysiology of depression as well (see "Role of Neurotrophins in Depression: Alterations of Neuroplasticity and Links with the Other Aetiopathological Hypotheses" section).

On the contrary, bipolar disorder (BD) is associated with (i) increased cAMP signal transduction, as shown by higher levels of $G\alpha_s$ protein, stimulated AC and PKA [25] and (ii) hyperactivity of the phosphoinositide system, as indicated by the rise of G protein coupled to phospholipase C (G_q), protein kinase C (PKC) activity and its association with RACK1 [26, 27]. In keeping with these findings, lithium as antipsychotic drug acts on second messenger systems.

To sum up, the major liability of the monoamine deficiency hypothesis is derived from the examination of the molecular mechanisms elicited by currently available antidepressants. However, approximately two thirds of patients have a clinical response to these agents, whereas one third show a response to *placebo* [28]; perhaps, the mechanisms of depression are not related only to monoamines but to other pathogenetic factors to be examined [29].

The Hypothalamic–Pituitary–Adrenal Axis in Depression: Involvement of Stress and of the Neuroendocrine System

Selye originally described stress as a non-specific response of the body to any demand placed upon it [30], and today, it is considered as an event or experience that threatens the ability of an individual to adapt and cope. As a result, the stressor evokes a stress response, which involves the release of hormones and other cellular mediators that may promote adaptation when the response is efficiently turned on and shut off but which also promote pathophysiological processes when the response is overused or dysregulated.

Stress is perceived by the brain cortex, transmitted to the hypothalamus leading to the HPA activation. HPA activity is regulated by adrenocorticotropic hormone-releasing factor (corticotropin-releasing factor (CRF)) and vasopressin (AVP) secreted from the hypothalamus, which in turn stimulates the pituitary to secret the adrenocorticotropic hormone (ACTH) that finally activates the secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex. Glucocorticoids then bind to their receptors localised within the HPA axis as well, where they exert a feedback control on CRF, AVP and ACTH secretion [31].

Glucocorticoids not only control peripheral functions like metabolism and immunity but have also several central effects: they regulate neuronal survival, neurogenesis, the sizes of hippocampus, the formation of new memories and the emotional assessment of events [32], being a key link between stress and brain functioning. Therefore, it is not surprising that several studies observed an increased activity of the HPA axis in depressed patients which showed (i) increased levels of cortisol in saliva, plasma and urine, (ii) increased level of CRF in CSF and in limbic brain regions and (iii) increased size (as well as activity) of the pituitary and adrenal glands (as reviewed by Nemeroff and Vale [33]). This HPA axis hyperactivation is likely related to alterations in the feedback inhibitory control by endogenous glucocorticoids [34].

In this regard, Carrol et al. [35] showed that the cortisol suppression response is absent in about half of the most severely depressed patients treated with the synthetic glucocorticoid dexamethasone, a drug that was used to evaluate the sensitivity of the hypothalamus to feedback signals for the

shutdown of CRF release. By contrast, a potent feedback inhibition of the HPA axis was induced even by a small dose of dexamethasone administered in healthy subjects, leading to reduced cortisol levels for 24 h. Interestingly, successful antidepressant treatments are associated with resolution of the impairment of glucocorticoid-induced negative feedback on the HPA axis [36].

In any case, only subgroups of depressed patients show HPA axis activation, suggesting that the interaction with genetic predisposition and adverse events (particularly in early life) would lead to vulnerable phenotypes characterised by amplified stress reactivity [37].

Depression and the Inflammatory Process

Early papers about inflammation and monocytic and T cell activation in depression were firstly published in 1990s. More recently, this standpoint has been reprised and MDD patients have been shown to exhibit evidence of inflammation, as manifested by increased concentrations in peripheral blood and CSF of inflammatory cytokines like tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6 [38]. Moreover, the acute phase proteins, chemokines and adhesion molecules were shown to be enhanced in peripheral blood of depressed patients [39], and Miller et al. [40] observed that the administration of cytokines [e.g. interferon-alpha (IFN-α)] and of cytokine inducers (lipopolysaccharide and typhoid vaccination) led to behavioural changes similar to those seen in depressed patients. Indeed, also Capuron and co-workers [41] compared cytokine-induced depressive syndromes with depression, reporting that only psychomotor retardation and anorexia were more frequent and/or severe in cytokine-treated individuals.

The molecular mechanisms by which cytokines may impact behaviour are manifold: cytokines may influence both the metabolism of NA, 5-HT and DA and the neuroendocrine functions, leading to flattening of the cortisol curve and increased evening cortisol concentrations [42, 43], suggesting the existence of a link between the "inflammasome" activation and HPA axis. In fact, several studies in rodents have also demonstrated that stress-induced decreases in BDNF and neurogenesis are related in part to the induction of innate immune cytokines [44]. Moreover, administration of both IFN-α and typhoid vaccination to humans may alter mood relevant neurocircuits including basal *ganglia* and dorsal anterior cingulate cortex, brain regions that control behaviours related to motor activity, motivation, anxiety and alarm reactions [45].

Much less attention has been paid to the potential role of the adaptive immune response (above all of T cells) in depressive disorders, even if it was shown that antidepressants and mood stabilisers inhibit cell-mediated immune responses and induce a Th-2 shift [46, 47]. First studies reported that proliferation of peripheral blood mononuclear cells in response to phytohemagglutinin and concanavalin A, i.e. T cell mitogens, was reduced in severe MDD in humans, as reviewed by Irwin et al. [48]. These early results have been confirmed also through meta-analytic approaches reaching the *consensus* that statistically reliable decreased T cell responses exist in both stressed and depressed individuals [48, 49].

Nevertheless, the mechanisms of T cell alterations have yet to be completely established. A hypothesis is that T cells of depressed patients undergo increased apoptosis, as revealed by flow cytometric studies [50]. This may occur (i) for tryptophan depletion, that is an essential proliferative *stimulus* for effector T cells [51]; (ii) by glucocorticoids, that induce apoptosis on immune cells, especially on developing ones in the *thymus* [52]; (iii) and by inflammatory cytokines [53].

Taken together, these observations suggest that the immune system could play a role in depressive disorders and new knowledge of the involved cell types and of their complex molecular mechanisms may be useful to detect easily available peripheral blood biomarkers, above all as predictors of therapy outcome [54].

Role of Neurotrophins in Depression: Alterations of Neuroplasticity and Links with the Other Aetiopathological Hypotheses

Since Cajal, a static view of the brain has prevailed in which electrical and chemical pieces of information were thought to be processed through a fixed system of neuronal circuits. This view has been gradually revised starting from various studies showing that neuronal circuits and connections are subject to lifelong modifications and reorganisations following external and/or internal *stimuli*. These dynamic modifications, the so-called neural plasticity, have been demonstrated in several experimental studies showing that exposure to stress may cause alterations in processes or number of neurons, atrophy of hippocampal CA_3 pyramidal neurons and decrease of cell proliferation in *dentate gyrus*.

Apart from these preclinical findings, also neuroimaging studies in depressed patients have demonstrated selective structural changes across various limbic and non-limbic regions: in prefrontal and cingulate cortex, both metabolism and volume are reduced, while hippocampal atrophy occurs with further syndrome progression [55, 56]. Moreover, post-mortem morphometric studies revealed decreased glial densities in some cortical and limbic brain areas [57]. Thus, depressive disorders may be associated with the impairment of structural plasticity and cellular resilience, and antidepressant medications may act by normalising this impairment [56].

In this context, neurotrophic factors like BDNF, nerve growth factor (NGF) and neurotrophin-3 are known to exert their actions not only during neuronal development and maturation but also in the adult brain, where their expression is regulated by several *stimuli* such as stress and psychotropic drugs. In fact, BDNF expression is downregulated by the

exposure to stress in *dentate gyrus*, CA_3 and CA_1 pyramidal cell layers [58] and this downregulation may contribute to the atrophy of CA_3 neurons and to the reduced neurogenesis of hippocampal granule cells, even if elevated levels of adrenal glucocorticoids could also account for these effects [59].

In contrast to the effects of stress, subchronic or chronic antidepressant administration increases the expression of BDNF both in hippocampus and in frontal cortex [59] and behavioural studies support the hypothesis that the BDNF upregulation may contribute to the therapeutical action of antidepressants. Siuciak et al. [60] showed that chronic infusion of BDNF in the midbrain exerted an antidepressant action in the forced swim and learned helplessness models, and Shirayama et al. [61] found that a single infusion of BDNF into the hippocampus produces a massive and long-lasting antidepressant effect in these behavioural models.

These studies suggest that BDNF is the link among stress, neurogenesis and hippocampal atrophy in depression. However, it has been highlighted in "The Monoaminergic Hypothesis of Depression" section that the gene of BDNF is upregulated by the transcription factor CREB, whose expression is stimulated by antidepressant treatments that increase NA and/or 5-HT concentrations in the synaptic cleft. Therefore, BDNF is also tightly linked to the monoaminergic hypothesis of depression. A summary of all these interplays between the various aethiopathological hypotheses is reported in Fig. 1.

Finally, BDNF may be considered as the link with the inflammatory hypothesis of depressive disorders as well, because signs of inflammation have been described both in MDD and in cardiovascular disease, and endothelial cell signaling plays a crucial role in cardiovascular disease and brain neurogenesis through the secretion of this neurotrophin (see "Depression and the Inflammatory Process" section). By the way, strong epidemiological data point to the association between MDD and increased cardiovascular morbidity and mortality [62] and antidepressants were shown to increase the survival rate among patients who become depressed after coronary occlusion [63].

Neuroimaging Abnormalities in Mood Disorders and the Mitochondrial Hypothesis

Alongside the classic pathogenetic hypotheses of depressive disorders, the need of new emerging theories in the perspective of overcoming the lack of response to pharmacotherapy in one third of patients has been discussed in the previous

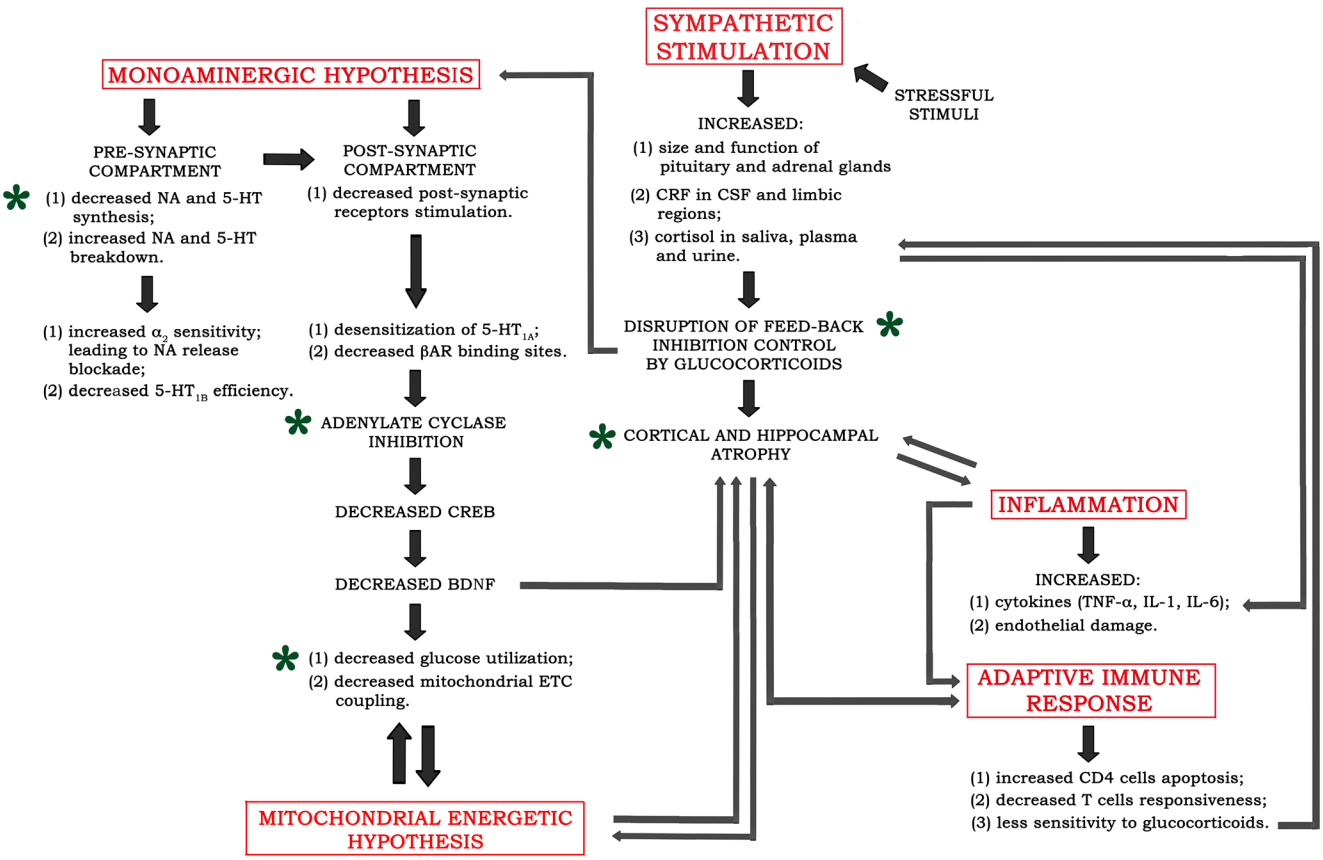

Fig. 1 Summary of the interplays between the aethiopathological hypotheses of depression

section. In the same context, a great interest has been recently put on the bioenergetic alterations detected in mood disorders, leading to formulate a mitochondrial pathogenetic hypothesis (Fig. 1). Actually, the concept "mitochondrial psychiatry" has been previously used in the title of a review about psychiatric symptoms in mitochondrial disorders and mitochondrial alterations in psychiatric disorders [64] and as chapter titles in a book and a review about mitochondrial medicine [65, 66].

In this paragraph, an overview will be firstly given about the breakthrough results obtained by neuroimaging in vivo studies in human patients, starting from observations on cerebral blood flow (CBF) and cerebral metabolic rate of glucose (CMR_{glu}). These studies allowed to assess the presence of brain energy metabolism abnormalities in MDD and BD. Progressively increasing the depth of analysis by the evaluation of the modifications of energy-linked metabolites and molecules (adenosine-5′-triphosphate (ATP)), the focus will be transferred from the tissue as a whole to neuronal cells. Following this logic, the mitochondrial dysfunctions in mood disorders will be then discussed.

Results of the Neuroimaging Studies in Depressive Disorders

Methodologically, energy metabolism in brain samples can be studied by three different approaches: (i) determination of the adenylate pool constituents (ATP, adenosine diphosphate (ADP), adenosine monophosphate (AMP)), phosphocreatine (PCr) and the relevant intermediates of glycolysis and Krebs' cycle, (ii) assessment of oxidative phosphorylation, electron transfer chain complexes, Krebs' cycle enzymes and ATPases; (iii) and establishing the ADP/O *ratio*.

Besides these classical biochemical methods, various other methods have been devised to study in vivo brain energy metabolism in humans, applying functional neuroimaging techniques, that do not directly measure synaptic activity but indirectly assess the signals resulting from activity-dependent energy metabolism [17].

Measurements of ^{18}[F]Fluorodeoxyglucose Uptake and Cerebral Blood Flow

The neuroimaging abnormalities found in MDD and BD generally have corroborated the hypotheses regarding the neural circuitry underlying depression, which initially were based on observations from the behavioural effects of lesions experimentally placed in experimental animals, as well as from the clinical manifestations of lesions or atrophy arising in the context of neurological disorders associated with major depressive episode (MDE) [67].

The regions most commonly affected in MDD were the prefrontal cortex, anterior cingulate *gyrus* and temporal lobe, with contrasting results in subregions of these areas, as reviewed by Moretti et al. [17] and exemplified in Fig. 2:

- Decreases of FGD and CBF in the dorsomedial, lateral and dorsolateral prefrontal cortex, subgenual prefrontal cortex, dorsal anterior cingulate cortex and hippocampus
- Increases in the left ventrolateral prefrontal cortex, amygdala and thalamus. The *amygdala* is the only brain region where the abnormalities of FDG uptake and CBF correlated with the severity of the depression as evaluated by Hamilton Scale [68]

Interestingly, neuromorphometric abnormalities appear to be correlated to MDD time of onset: in patients with early-onset mood disorders, they were observed in the orbital and

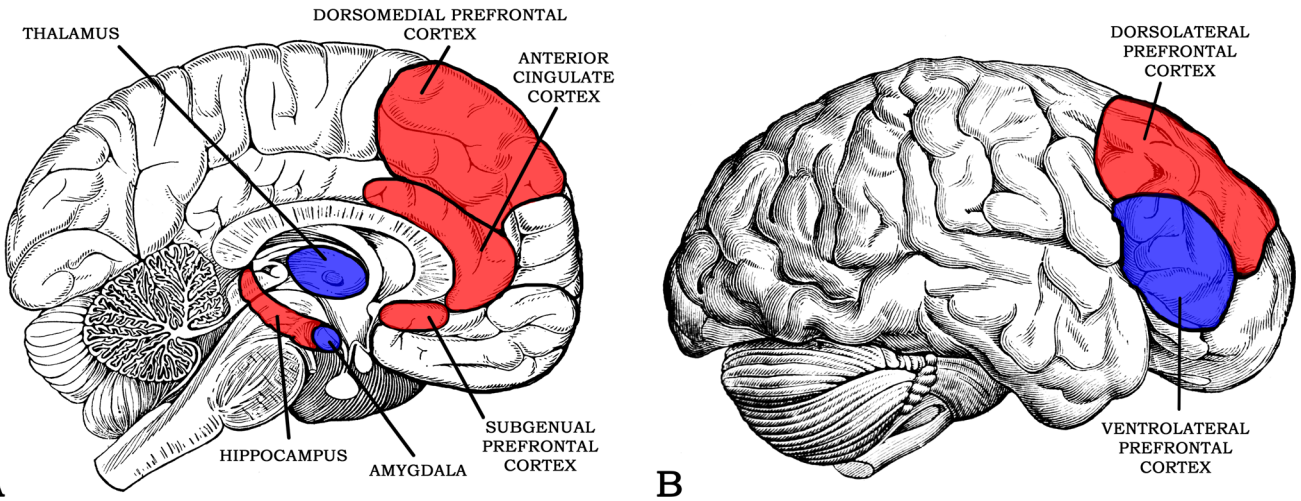

Fig. 2 Differential modifications in brain energy metabolism as assessed by ^{18}[F]fluorodeoxyglucose uptake and cerebral blood flow changes in neuroimaging studies on human depressed patients. In *blue areas*, the energy metabolism is increased; in *red areas*, it is decreased

medial prefrontal cortex and in anatomically related structures within the temporal lobe, striatum, thalamus and posterior cingulated [69]; by contrast, elderly subjects with late-onset depression showed higher correlation with cerebrovascular disease, both compared to age-matched healthy controls and to elderly depressives with an early age at depression onset [70].

As regards BD, findings are less clear, SPECT studies observing lower CBF in the frontal and temporal cortex in BD patients, particularly in the left hemisphere [71]. Overall, the frontal cortex seems to be hypoactive in depression, whether unipolar or bipolar [72].

N-Acetylaspartate as Marker of Mitochondrial Dysfunction

PET and SPECT provide an indirect assessment of metabolic brain activity. As previously pointed out, more direct information can be obtained by measuring brain metabolites in vivo with MRS. Some of the earliest MRS findings in support of a mitochondrial dysfunction hypothesis of mood disorder are the repeated observations of decreased cerebral *N*-acetylaspartate (NAA) in depressed patients.

As the most prominent metabolite peak on the ^{1}H *spectrum*, NAA levels are typically reported as a *ratio* using the total creatine signal (creatine *plus* phosphocreatine, Cr + PCr) as an internal reference peak (NAA/Cr + PCr). In healthy individuals, NAA is present in the brain at concentrations of 8–10 mM [73] and thus follows glutamate as the second most abundant amino acid in CNS. NAA synthesis occurs in mitochondria by the membrane-bound enzyme L-aspartate *N*-acetyl-transferase, is energy dependent and stimulated by ADP.

NAA seems to play a role in providing carbons for lipid and myelin formation [74] and protecting neurons against osmotic stress [75]; moreover, NAA may serve as a readily available precursor of *N*-acetyl aspartyl glutamate (NAAG), a molecule with neurotransmitter-like properties [76]. Madhavarao et al. [77] have proposed a model in which the synthesis of NAA is part of the "mini citric acid cycle". In this process, the extra demand for ATP in neurons could be met thanks to the oxidation of glutamate via the glutamate-oxaloacetate transaminase pathway and, by converting the aspartate produced in this cycle into NAA, NAA biosynthesis is thought to help in steering the reaction toward continuing energy production. Additionally, NAA is able to act like citrate as an acetate carrier to the cytoplasm, since citrate is not produced during the mini citric acid cycle. In this way, NAA is hypothesised to play an integral role in the energetics of neuronal mitochondria [78]. Consequently, decreased levels of NAA are more consistent with impaired mitochondrial energy production respect to neuronal death [79]; in fact, abnormally low *ratio*s of NAA in studies using mitochondrial respiratory chain inhibitors were shown to be correlated with decreases in O_2 consumption and ATP production [80].

It is of interest that most studies have found negative results for the involvement of NAA in the pathophysiology of MDD, even if some reports indicated an increase of NAA resonance by antidepressant treatments [81]. In keeping with this, Van der Hart et al. [82] reported that chronically stressed animals showed significantly NAA decreased concentrations, having antidepressants the ability to revert that decrease. Nevertheless, Yildiz-Yesiloglu and Ankerst [83] found in a meta-analysis about ^{1}H-MRS studies that MDD patients have similar NAA/Cr and NAA values to those of healthy controls in the basal *ganglia* and frontal lobes. This finding parallels the observation of normal neuronal cell numbers in MDD [84].

Otherwise, a number of ^{1}H-MRS studies have demonstrated reduced NAA levels in patients with bipolar disorder compared to normal controls (review by Stork and Renshaw [78]), particularly in the dorsolateral prefrontal cortex [85] and hippocampus [86], and a negative correlation exists between NAA/Cr + PCr or NAA levels and illness duration [87], implying that reductions in NAA levels in bipolar subjects may become more pronounced with time. In contrast with the majority of published MRS research on BD, the study by Deicken et al. [88] reported increased thalamic NAA in male bipolar subjects respect to controls. However, except two of the bipolar subjects, all patients were taking maintenance medications such as lithium and divalproex, which may have contributed to the observed increases in thalamic NAA. Alternatively, considering that the concentration of thalamic monoaminergic synaptic terminals is increased in BD [89], the increased thalamic NAA could be due to the enhancement of synaptic density rather than of metabolic abnormalities or to glial cell hypoplasia in the thalamus.

Decreased High-Energy Compounds

^{31}P-MRS allows researchers to perform non-invasive, in vivo measurements of other brain metabolites, including phosphomonoesters (PMEs), phosphodiesters (PDEs, i.e. membrane phospholipids), inorganic phosphate (P_i), PCr and α-, β- and γ-nucleoside triphosphate (α/β/γ-NTP). ^{31}P-MRS spectra of the brain typically show these substances as seven separate peaks. PCr and α/β/γ-NTP will be firstly discussed; PME and PDE findings will be summarised in "Impaired Phospholipid Metabolism" section.

PCr is a high-energy phosphate that is more concentrated in tissues with high-energy consumption (brain and muscle), and it is formed from ATP and creatine, with the catalyst creatine kinase (CK). PCr has a buffering role, transferring a high-energy phosphate group to ADP and re-forming ATP.

During periods of acute neuronal activity, as molecules of ATP are utilised by Na^+, K^+ and ATP-ase, PCr is rapidly broken down in order to maintain the overall concentration of ATP. Although short-term decreases in PCr concentration

indicate immediate cell activity, as can be observed in episodes of photic stimulation [90], long-term abnormalities in PCr concentration generally reflect much larger alterations in cellular metabolism and in particular an insufficient supply of the ATP needed for normal neuronal function.

Kato and collaborators [91] evaluated a 30-mm coronal slice between the frontal pole of the cortex and the anterior part of the *corpus callosum*. In a sample that included both MDD and bipolar subjects, they found PCr was significantly decreased in severely depressed patients (11.9 % of total brain phosphates) and in mildly depressed ones (13.5 % of total brain phosphates). Pettegrew et al. [92] reported that in two MDD subjects, PCr values in the prefrontal lobe increased significantly after successful treatment and were correlated with Hamilton Rating Scale for Depression (HAM-D) scores.

In BD, PCr was consistently decreased in depressive, euthymic and manic states [93], but its concentration was asymmetrical in medicated patients, being lower in the left than in the right frontal lobe during depressive states and the reverse in euthymic and manic states [94]. Interestingly, also CBF was observed to be decreased in the left hemisphere of BD patients. Overall, these studies lead to the observation that the concentration of PCr was lower in depressive states, whether in MDD or BD patients.

As regards nucleoside triphosphates, the brain NTP resonance is derived primarily from ATP but also includes other NTPs (e.g. cytidine and guanosine triphosphates). In the brain, ATP is present at much higher concentrations compared to other NTPs, and thus the α/β/γ-NTP peaks measured with ^{31}P-MRS primarily reflect the brain concentration of ATP. Nucleoside diphosphates (NDP) also contribute to the α and γ peaks, whereas the β peak is unique to NTP.

Although negative results in BD patients [95], Moore et al. [96] found that basal *ganglia* β-NTP was 16 % lower in MDD subjects compared to normal controls, and Volz and colleagues [97] reported decreased total ATP (by 7.6 %) and a very significant decrease of β-ATP (by 16.9 %) in MDD patients compared to controls.

Also Renshaw et al. [98] found that white matter and basal *ganglia* β-NTP concentrations were 33 % lower in depressed subjects compared to normal controls, remarkably showing a positive correlation with severity of depression at baseline as assessed by the HAM-D scores. Moreover, subjects who responded to antidepressant treatments had lower baseline levels of β-NTP compared to non-responders, suggesting that the "response to treatment may be predicted by the result of MRS" and "agents that increase the brain levels of ATP may have antidepressant efficacy" [98].

Impaired Phospholipid Metabolism

In brain cells, the synthesis and maintenance of the cell membrane require between 10 and 15 % of net brain ATP production. Therefore, alterations in membrane phospholipids may be indirectly indicative of energy metabolism impairment: if less energy is produced in the cell, it is likely that aspects of phospholipid metabolism would also be impaired. Indeed, many MRS studies have evidenced some abnormalities in phospholipid metabolism in mood disorders, as indicated by alterations in the levels of choline compounds, *myo*-inositol, inositol monophosphates and PMEs.

As regards choline compounds, ^{1}H-MRS studies indicated increased choline signals in MDD patients [99], although Yildiz-Yesiloglu and Ankerst [83] did not find positive results in a following meta-analysis of ^{1}H-MRS literature. However, elevated Cho/Cr + PCr *ratio*s and Cho concentrations were observed in bipolar patients compared to healthy controls, particularly in the basal *ganglia* [100]. Remarkably, significant increases in choline resonance are commonly observed in neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis, as well as in cases of ischaemia and head trauma [101], indicative of membrane breakdown, but also of mitochondrial dysfunction.

Meta-analyses found similar *myo*-inositol values between adult MDD patients and controls in the frontal lobe structures [86], even though in CSF it was markedly reduced in depressed patients with unipolar or bipolar affective disorder [102]. In BP, *myo*-inositol has most often been examined respect to its apparent involvement in the mechanism of action of lithium, a potent non-competitive inhibitor of inositol-1-phosphatase that leads to an accumulation of inositol-1-phosphate and a simultaneous decrease in levels of *myo*-inositol [103].

Because of the widespread use of lithium, there are few MRS data from bipolar subjects that can be analysed without regard to its effects: Davanzo et al. [104] reported increased *myo*-inositol/Cr + PCr levels in the anterior cingulate of children and adolescents who had never been treated with lithium, when compared to normal controls; Winsberg et al. [85] found in bipolar patients (drug-free for at least 2 weeks before examination) a nearly significant trend toward higher levels of *myo*-inositol/Cr + PCr in the right dorsolateral prefrontal cortex of bipolar subjects versus controls. *Myo*-inositol involvement in mood disorders is thus controversial even up to date.

Finally, as regards PMEs, Kato et al. [92] reported no differences in PME levels between MDD subjects and normal controls, while Volz et al. [97] reported decreased PME, especially in the left brain of MDD patients compared to normal controls. This finding is consistent with a decreased turnover of membrane phospholipids and increased concentrations of phospholipid precursors. The situation seems to be more complex in BD: unlike many MRS findings in bipolar patients, some researches on PME concentration indicate the possibility of state-dependent changes, being PME levels decreased in euthymic bipolar subjects, as reviewed by Stork and Renshaw [78].

Thus, several pieces of evidence exist on impaired phospholipid metabolism in mood disorders, even if showing a complex pattern according to the considered pathological state.

Glutamate Alterations and Relationship with Brain Energy Metabolism

Glutamate is not only a neurotransmitter but also a metabolic intermediate that may derive (i) from the reductive amination of α-ketoglutarate by glutamate dehydrogenase, (ii) from transamination reactions catalysed by glutamate-oxaloacetate transaminase and glutamate-pyruvate transaminase and (iii) from glutamine by glutaminase-catalysed reaction after the glutamate released from nerve terminals has been converted to glutamine by glutamine synthetase at first [105].

As regards the glutamatergic hypothesis of depression in terms of receptor involvement, the non-competitive, glutamatergic *N*-methyl-D-aspartate (NMDA) antagonist (R,S)-ketamine has demonstrated an antidepressant efficacy within hours after a single administration, improving core depressive symptoms in the treatment-refractory unipolar and bipolar patients at subanaesthetic doses and this action persists on average for 1 week. However, the clinical use is limited owing to its abuse liability and dissociative effects at low doses [106]. Moreover, the results of human treatment trials indicate that alternative NMDA receptor antagonists lack the antidepressant properties [107].

In any case, the strategy of blocking with ketamine the NMDA receptors and the ensuing signalling cascade is still pursued as underlined by the hypothesis related to the involvement of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors in the action of norhydroxyketamine, that is the putative active metabolite of ketamine [108]. In fact, recent data provide evidence that the antidepressant effects of ketamine implicate an NMDA receptor inhibition-independent mechanism. The metabolism of (R,S)-ketamine to (2S,6S;2R,6R)-hydroxynorketamine is essential for its antidepressant effects because the administration of the (2R,6R)-hydroxynorketamine enantiomer induces an acute increase in glutamatergic signalling, followed by a long-term adaptation involving the upregulation of synaptic AMPA receptor, as shown by an increase in GluA1 and GluA2 in hippocampal synapses [108].

A number of ^{1}H-MRS investigations have reported increased levels of glutamate *plus* glutamine signal (Glx) in the frontal lobes, basal *ganglia*, left dorsolateral prefrontal cortex (DLPFC) and global grey matter of drug-free bipolar subjects [109], likely implying alterations in the glutamate/glutamine cycle. However, the limited available number of studies in MDD patients indicated lower Glx values in the frontal lobes respect to healthy controls. Thus, while a hyperglutamatergic state in bipolar disorder is probable, a hypoglutamatergic state in unipolar disorder is more likely.

Consistently with this observation, lower γ-amminobutyric acid (GABA) levels were observed in plasma and CSF of MDD patients [110], increasing after antidepressant treatments. GABA concentration decrease may result from reductions in GABA synthesis because of the decreased glutamatergic stimulation of metabolic activity and because of the reduced concentrations of glutamate for GABA synthesis by glutamate decarboxylase [83]. Moreover, Nowak et al. [111] showed a reduced high-affinity binding to NMDA receptors in the frontal cortex of suicide victims compared with matched controls and also found that some antidepressants produce alterations in the NMDA receptor complex, suggesting that the pathophysiology and treatment of depression may involve glutamatergic pathways [112, 113].

By the way, the hyperglutamatergic state in bipolar disorder may correlate to the decreased intracellular pH observed in bipolar patients. As suggested by Dager et al. [109], increased levels of brain glutamate would entail abnormal high demands on neuronal energy metabolism, similar to (but less severe than) the excitotoxic mechanism of cell death that occurs during stroke. If cells are unable to meet such increased energy requirements through mitochondria-based oxidative phosphorylation, rates of glycolysis would increase, thus causing the increased levels of lactate and decreased pH observed in BD studies.

Final Considerations About Neuroimaging Studies

The studies cited in this section underline the importance of neuroimaging techniques in addressing the important issue of energy metabolism in mood disorders. Nevertheless, some drawbacks exist: the lack of tridimensionality of the obtained images and the limited resolution capacity, in particular of ^{31}P-MRS. In fact, ^{31}P-MRS possesses relatively low sensitivity, approximately 5 % of that of hydrogen (^{1}H, proton) MRS [114]; thus, at 1.5 T, typical phosphorus and proton MRS voxels are on the order of 25–100 and 1–10 cm^{3}, respectively.

For their wide availability, 1.5-T systems are currently used for the majority of neuroimaging studies in humans, even if the development of MRS methodology coincided with the introduction of higher magnetic fields, and one of the seminal studies describing MRS in the human brain for the first time was performed at 4 T [115]. However, in animal models, higher magnetic fields (4.7 and 9.4 T) have been widely used and the number of available high field (3 and 4 T) MRS for human studies is increasing as well: Robitaille et al. [116] demonstrated that clinical imaging will be possible even at 8 T.

However, increasing the electromagnetic field energy to such a degree may have consequences on the brain tissue and may affect the results. In this context, the studies on brain mitochondria (that will be discussed below) are of particular

interest because they allow to evaluate bioenergetic changes, overcoming the previously reported issues concerning neuroimaging techniques, which remain in any case important to confirm the reliability of the results obtained in mitochondrial studies and the feasibility of translating them "from bench to the bed side".

The Mitochondria: *Domini Vitae Necisque*

The Latin title above [117] may sound quite impressive but mitochondria are actually the "masters of life and death" since, in mammalian tissues, up to 90 % of ATP, i.e. the primary energy substrate of biological systems, is generated by mitochondria, and this consideration is relevant above all for the central nervous system.

The importance of ATP as energy source is given by the fact that, in all tissues, the Gibbs energy change for cellular syntheses, mechanical work and active transport is usually calculated by the equation:

$$\Delta_r G'_{\text{ATP-hyd}} = \Delta_r G'^{0}_{\text{ATP-hyd}} + RT\ln\left(\frac{[\text{ADP}][\text{P}_\text{i}]}{[\text{ATP}]}\right)$$

where $\Delta_r G'_{\text{ATP-hyd}}$ is the transformed Gibbs energy of reaction referred to the biochemical reaction of ATP hydrolysis; $\Delta_r G'^{0}_{\text{ATP-hyd}}$ is the transformed standard Gibbs energy of reaction referred to the biochemical reaction of ATP hydrolysis; R is the ideal gas constant (8.314 JK^{-1} mol^{-1}); and T is the absolute temperature (−273.15 °C) [118].

As regards the CNS, ATP is fundamental because the brain is metabolically one of the most active organs in the body, since it accounts for only 2 % of body weight but about 20 % of resting total body O_2 consumption and 25 % of that of glucose. O_2 is utilised almost entirely for glucose oxidation: the resulting energy is transferred for the synthesis of "high-energy phosphate" bonds in the ATP molecule. Only 40 % of the energy released from glucose can be used for metabolic pathways since about 60 % is lost as heat and entropy. Therefore, the efficiency of the energy transducing pathways is low and should be maximised at its best, being the neuronal activity closely coupled to energy metabolism: energy requirements are in fact particularly high for the activities of Na^+, K^+ ATP-ase, Ca^{2+} ATP-ase and other ATP-ases in plasma and endoplasmic membranes [119].

In most energy-consuming processes, the free energy donor is ATP, an energy-rich molecule that owes this feature to two phospho-anhydride bonds. A large amount of free energy is released when ATP is hydrolysed to ADP and orthophosphate (P_i) or AMP *plus* pyrophosphate (PP_i). In both reactions, the standard free energy change ($\Delta G'^{0}$) is −7.3 kcal/mol [120].

The brain concentration of ATP is low (≈2 mM), but its turnover is very high. Therefore, the possibility of the adenylate system acting as an energy mediator depends closely on the rate of ATP resynthesis: (i) from other "high-energy phosphates", such as PCr, a *reservoir* of high-energy phosphoryl groups that can be readily transferred to ATP through the reaction catalysed by CK; (ii) through anaerobic glycolysis in the cytosol, a sequence of reactions converting glucose into pyruvate with net generation of two molecules of ATP from ADP for each molecule of glucose; and (iii) through aerobic mitochondrial processes, i.e. Krebs' cycle, and the final pathway of pyruvate oxidation to CO_2 and H_2O with the synthesis of ATP from ADP + P_i by oxidative phosphorylation, the major source of ATP [17].

Mitochondria also play a major role in regulating (i) cellular free Ca^{2+} which they can accumulate when its concentration rises above critical values, (ii) the apoptotic process and (iii) neuroplasticity.

Mitochondrial Ca^{2+} uptake from and release into the cytosol have important consequences for neuronal and glial activity, modulating both physiological and pathophysiological intracellular responses [121]. Moreover, a large movement of positively charged Ca^{2+} into the mitochondrion will exert a depolarising effect: this increase can overcome mitochondrial capacity to export protons (as well as other cations), leading to the termination of ATP synthesis and the initiation of apoptosis [122]. In fact, mitochondria play a pivotal role in intrinsic pathway of apoptosis [123, 124].

As reviewed by Forbes-Hernández et al. [125], the activation of this pathway of apoptosis is induced by changes in the inner mitochondrial membrane resulting in the opening of the mitochondrial permeability transition pore (MPTP). Through this, the following are released: (i) cytochrome *c* that promotes the caspase cascade through the formation of the apoptosome by the aggregation and activation of caspase-9 with apoptotic protease activating factor 1 (Apaf-1); (ii) the complex Smac/DIABLO that promotes apoptosis by inactivating the inhibitors of apoptosis proteins (IAP); (iii) apoptosis-inducing factor (AIF) that promotes chromatin condensation and DNA degradation; and (iv) endonuclease G and (v) caspase-activated DNAse that cleave nuclear chromatin.

Mitochondria sustain the cellular and tissutal homeostasis also because they serve as signalling platforms for regulating autophagy [126, 127], i.e. a caspase-independent process characterised by the early degradation of organelles, while the cytoskeleton remains conserved until the final phase of the dying process [128]. Interestingly, a recent study has pointed out that the autophagy-related signalling pathway PI3K-Akt-mTOR is related to mood disorders, being AKT1/mTOR mRNA expression observed in short-term bipolar disorder [129]. Moreover, both amitriptyline and citalopram (but not venlafaxine) have been reported to increase the expression of the autophagic markers LC3-II and beclin1 [130], also the co-chaperone FKBP5/FKBP51, that seems to act as an antidepressant and play a role in autophagy [131].

Considering that neurons are post-mitotic cells, basal autophagy should be highly regulated also because of its importance in neuronal morphogenesis, synaptogenesis, developmental and synaptic plasticity and axogenesis. In the same context, mitochondrial distribution and activity are themselves key factors for these processes: mitochondria are accumulated at sites where ATP consumption and Ca^{2+} concentration are higher and in the regions of growing axons [132], being NGF one of the attractant signals [133]. In addition, dendritic mitochondria are essential in the morphogenesis and plasticity of spines and synapses [134]: these findings suggest roles for mitochondria as mediators of at least some effects of glutamate and BDNF on synaptic plasticity [133] and, on the other hand, BDNF was found to increase glucose utilisation and mitochondrial respiratory coupling at ETC complex [135].

Mitochondrial Genetic Abnormalities and Impairments of Protein Synthesis and Functions

Mitochondria are the only organelle to contain non-nuclear genetic information but also copies of mitochondrial DNA (mtDNA), composed by 16,569 bp. MtDNA encodes two ribosomal RNAs, 22 transfer RNAs, 13 protein subunits of the electron transport chain and the displacement loop (D-loop), which is necessary for replication and transcription of the mitochondrial genome. At least 1000 nuclear-encoded proteins are also translocated into mitochondria, and the interactions between both mitochondrial proteins and translocated proteins are required for normal cellular function.

Mitochondria have the unique properties of heteroplasmy and maternal inheritance. Heteroplasmy refers to the fact that different cells contain different numbers/types of mitochondria; thus, mitochondrial dysfunction may manifest in a very regional-specific manner. MtDNA is inherited maternally, being present in low concentrations in spermatozoa (about 1200 copies in a single spermatozoon), compared to oocytes (about 100,000 copies in a single oocyte). It is noteworthy that some previous studies have noted a parent-of-origin effect in BD [136] even if failure to find a pattern of maternal inheritance, as well as evidence of paternal inheritance, has been reported [137].

Although mtDNA mutations may be maternally transmitted, they are often sporadic. MtDNA is more susceptible to somatic deletions than nuclear DNA because mtDNA is not protected by histones and also has a poor DNA repair system. Thus, mtDNA has been suggested as a potential "weak point" of the genome: in particular, a 4977-bp deletion (also known as the "common deletion") is the most frequent abnormality in patients with mitochondrial myopathies and during ageing [138].

As regards depressive disorders, several studies have pointed out the relationship with mitochondrial dysfunction, even if the common 5-kb mtDNA deletion could not be detected in post-mortem brain from subjects with probable or diagnosed MDD [139, 140]. On the other hand, alterations of translational products linked to mitochondrial function were found in the frontal, prefrontal and tertiary visual cortices of MDD patients [141], along with the decreased gene expression of 6 of 13 mtDNA-encoded transcripts in frontal cortex tissue [140] and of nuclear DNA-encoded mitochondrial mRNA and proteins in the cerebellum [142]. However, a few microarray studies in MDD have not reported that mitochondrial genes were differentially expressed in cortex [143, 144].

Furthermore, in MDD, alterations of four mitochondrial-located proteins in the anterior cingulate cortex have been reported [145], and mRNA and protein levels of electron transport chain complex I subunits (NDUFV1, NDUFV2, NADUFS1) were altered in striatal and lateral cerebellar hemisphere post-mortem specimens of both MDD and BD patients, albeit in a disease-specific neuroanatomical pattern [142]. The depressed group showed consistent reductions in all three subunits in the *cerebellum*, while the bipolar group showed increased expression in the parieto-occipital cortex (similar to those observed in schizophrenia) and reductions in the *cerebellum*, yet less consistent than the depressed group.

Andreazza et al. [146] found another complex I subunits (NDUFS7) to be below or at the lowest range of the normal controls in post-mortem prefrontal cortex. Decreases of respiratory chain enzyme *ratios* and ATP production rates were also found in muscle from patients with a lifetime diagnosis of MDD with concomitant physical symptoms [147].

Notably, Konradi and collaborators [148], in a series of post-mortem brain microarray, found that 42 % of the genes that were reduced in BD hippocampi coded for mitochondrial proteins involved in regulating oxidative phosphorylation in the mitochondrial inner membrane, as confirmed subsequently also by Sun et al. [149]. In addition, Benes et al. [150] showed a marked downregulation of antioxidant genes in BD. These authors suggested that accumulation of free radicals might then occur in the setting of the previously reported decrease of the electron transport chain.

Even though inhibition of complexes I, III and IV of mitochondrial electron transport chain was observed also in the chronic mild stress animal model in cerebral cortex and hippocampus [151], these observations should be taken with caution, since numerous potentially confounding factors may lead to misinterpretation of results: ante-mortem medication history, substance abuse/dependence, comorbidities (often seen in BD subjects), post-mortem interval and cause of death. At this regard, it is important to note that the phosphorylation state of proteins is extremely sensitive to post-mortem interval [152], as are decreased tissue pH and increased RNA degradation [153]. So, observed changes could be related to the disease, or to agonal factors, or be due to post-mortem changes [122].

In any case, several studies have reported modifications in brain bioenergetics and mitochondrial function after drug

treatment, indicating that antidepressants seem to be partial inhibitors of mitochondrial function and respiration.

For example, fluoxetine in vivo administration showed stimulation of rat liver mitochondrial respiration in state 4 for α-ketoglutarate or succinate oxidations in acute or prolonged treatments (1 h after a single i.p. dose of 20 mg/kg b.w. and 22 h after 12 days of treatment with a daily dose of 10 mg/kg b.w., respectively), indicating uncoupling of oxidative phosphorylation [154]. This uncoupling effect of oxidative phosphorylation by the drug has been described also for rat brain mitochondria and for TCAs and other psychotropic drugs [155–157]. In this regard, Curti et al. [158] reported that fluoxetine decreased the rate of ATP synthesis and depressed the phosphorylation potential of rat brain mitochondria in vitro, likely interfering with the physical state of lipid bilayer of inner mitochondrial membrane.

However, the potential ETC inhibition by antidepressants is debated, and it cannot be excluded that the previous observations are misinterpretations of obtained data: for example, acute in vivo administration of amitriptyline in mice caused a decrease in brain content cytochrome oxidase evaluated by histochemistry [159], leading to suppose an uncoupling of ETC efficiency. Nevertheless, this is a quantitative structural result not reflecting the activity of the enzyme, i.e. of the functional parameter. By the way, 1 and 2 weeks of i.p. treatment with imipramine at the dose 10 mg/kg t.d. stimulated state 3 and state 4 respiration rate in rat brain mitochondria, increasing also the intramitochondrial content of cytochrome *b* and $c + c_1$ in the first week of treatment and that of aa_3 cytochrome in the second week [160]. Nortriptyline even proved neuroprotective in vitro in the oxygen/glucose deprivation ischaemia model and in vivo decreased infarct size and improved neurological scores after middle cerebral artery occlusion in mice [161].

Thus, even if the effects of antidepressants on mitochondrial functions have been studied for a long time and the neuroimaging studies confirm the involvement of bioenergetic abnormalities in mood disorders' pathophysiology and treatment, a *consensus* on this issue has not been reached yet. These conflicting results may be accounted by a variety of factors, including (i) misinterpretation of obtained data, as previously underlined; (ii) biases in experimental study design, e.g. considering whole brain homogenates and/or mitochondria, not taking into account the macroheterogeneity of brain areas as regards the bioenergetic changes in depressed patients (see "Results of the Neuroimaging Studies in Depressive Disorders " section); (iii) the assumption that in vitro addition of drugs is comparable to in vivo administration; and (iv) the lack of ex vivo analyses at subcellular level.

In particular, this latter point is quite striking because antidepressants possess clear-cut differential effects on pre-synaptic nerve endings and on post-synaptic terminals, i.e. on different subcellular compartments. This limitation may be overcome by the isolation of the mitochondrial populations differently distributed in neurons according to the analytical subfractionation technique developed by us [31, 162–164], which allows to separate (i) the non-synaptic mitochondria, i.e. the mitochondrial population of neuronal perikaryon related to post-synaptic neuronal compartment, from (ii) the intra-synaptic mitochondria located in vivo in synapses and related to the pre-synaptic compartment. Apart from their localisation, these mitochondria are different especially because the Gibbs free energy ($\Delta G^{0\prime}$) produced by non-synaptic mitochondria is directly linked to protein synthesis, while that of intra-synaptic ones is mainly linked to ion homoeostasis and neurotransmission at the synapse.

By taking into account the microheterogeneity of the brain mitochondria populations, it would be possible to cast new insights into the molecular mechanisms of action of antidepressant drugs, as our recent encouraging results seem to suggest [165]: we observed that subchronic desipramine and fluoxetine treatments in 10-week-old healthy rats have led to (i) the enhancement of cytochrome oxidase activity on non-synaptic mitochondria and (ii) to the decrease of malate, succinate dehydrogenase and glutamate-pyruvate transaminase activities of intra-synaptic ones, indicating different effects exerted by both drugs on pre- and post-synaptic compartments, in perspective highlighting new antidepressant therapeutical strategies targeting brain energy metabolism. In fact, another important open question is that all the approved antidepressant drugs rely upon the monoaminergic hypothesis of affective disorders that, however, is based mainly on the acute neurochemical effects of these drugs, usually occurring within minutes after a single dose administration. Remarkably, clinical improvements are observed only following 1 to 3 weeks of continuous administration, as it is known for a long time [166]. In this regard, recent theories have extended the mechanism of antidepressant response to signal transduction pathways that have been shown to be impaired in depressed patients (see "The Monoaminergic Hypothesis of Depression" section).

In particular, changes found in *pre-synaptic* protein phosphorylation and in the release machinery after antidepressant treatments are likely to be the molecular correlates of the changes observed in neurotransmitters' release [167]. The first question is whether pre-synaptic changes are caused by desensitisation of pre-synaptic terminal auto- and hetero-receptors. Indeed, it was shown that the modulatory action of pre-synaptic receptors on neurotransmitters' release may be accounted by the G protein-mediated modulation of ion channels, as well as by a direct action on pre-synaptic release machinery [168].

It is likely that changes in monoamine pre-synaptic terminal inhibitory receptors, such as 5-$HT_{1B/D}$, α_2, and D_2 receptors, may affect the release by acting on local pre-synaptic mechanisms: one way by which these receptors exert their

action is by affecting AC, the cAMP signalling pathway, PKA activity and eventually the phosphorylation of voltage-activated calcium channels and potassium channels [169]. Thus, the stimulation of receptors by increased synaptic monoamine levels may initially decrease cAMP production, because these receptors are negatively coupled to AC. This will decrease PKA activity and, in turn, increase potassium and decrease calcium conductance, with consequent hyperpolarisation of the pre-synaptic terminal and decreased probability of release. Successive desensitisations of terminal receptors may attenuate this action on ion channels and membrane potential, inducing the change in CaMKII-dependent phosphorylation of vesicular effectors (synaptotagmin, synapsin I), whereby facilitating transmitter release [170].

In addition to these pre-synaptic events, also *post-synaptic* adaptations take place and, as regards the delayed therapeutic effects of antidepressants, the more reliable hypotheses are linked to the fact that post-synaptic monoaminergic receptors are (i) desensitised in their responsiveness ability, because of the persistent lack of stimulation by their endogenous ligands, depleted in depressive states, or (ii) downregulated in their number. To sustain the latter hypothesis, it should be remembered that (i) the synthesis of a protein of n amino acids requires the consumption of $n - 1$ molecules of ATP, just to activate each amino acid [17], and (ii) the synthesis de novo of receptors is both energy- and time-consuming, explaining the time lag between the pharmacological and therapeutical action of these drugs.

Concluding, both pre-synaptic and post-synaptic events after long-term antidepressant treatments require a great amount of energy, to be employed properly to exert the therapeutic effects of drugs. These considerations sustain the mitochondrial hypothesis of depression, which states that impaired energy metabolism of brain cells is involved in the pathophysiology of mood disorders and in the effects of antidepressants and mood stabiliser drugs.

Conclusions and New Perspectives

It is generally accepted that the pathogenesis of affective disorders and the therapeutical effects of antidepressants are related to adaptive mechanisms of neurotransmitter systems, identified with the intracellular signalling cascades which eventually mediate the physiological responses. The involvement of long-lasting events (i.e. regulation of gene expression) has been convincingly argued as well. However, these molecular and cellular changes are likely only the epiphenomenon of more subtle and to-date unknown alterations, because of the lack of response to current pharmacotherapy in one third of patients.

Considering all the aethiopathological hypotheses of depression so far proposed from an integrated point of view (Fig. 1), the involvement of stress-activated pathways seems to be the *primum movens* leading to CNS adaptations and to the known molecular and cellular findings in depression. This hypothesis is supported evaluating the functional connections between the cerebral areas linked to the stress responses and neuroendocrine system, summarised in Fig. 3.

In physiological conditions (grey lines), sensory data arrive to thalamus that acts like a switchboard, sending these pieces of information directly to the amygdala (low-road pathway) and to the cerebral cortex, in particular to the anterior cingulate cortex and to the prefrontal cerebral cortex (high-road pathway) [171]. The role of these circuits is to maintain the proper homeostatic amygdala activation, being the low-road pathway activating and the high-road pathway inhibiting. In addition, amygdala quickly processes the received data and activates the hippocampus, establishing a feedback loop between the two areas providing a reference point to the memory and emotions of past experience [172]. If the stressful inputs are higher than usual, the amygdala eventually leads to the hyperactivation of the HPA, resulting in ACTH and glucocorticoids release. Remarkably, glucocorticoids receptors are highly expressed in all these cerebral areas so to grant a feedback inhibitory control [173–176].

Interestingly, also the previously reported neuroimaging abnormalities related to the energy metabolism found in depressed patients (see "Measurements of 18[F]Fluorodeoxyglucose Uptake and Cerebral Blood Flow" section) are mainly related to these cerebral areas (red arrows). In particular, in the complex pattern of the detected bioenergetic abnormalities, the following neuroimaging findings can be summarised: (i) the thalamus and amygdala are hypermetabolic, while (ii) the anterior cingulate cortex and prefrontal cortex are hypometabolic. As a consequence, in depression, the control exerted by the cerebral cortex and hippocampus toward the amygdala is lacking, and a persistent stress-activated *status* is likely established. The persistent

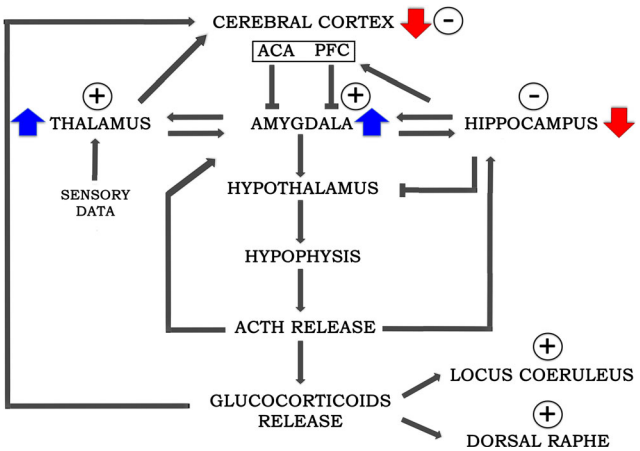

Fig. 3 Functional connections between the cerebral areas linked to the stress response and neuroendocrine system. *Blue arrows* indicate the areas where energy metabolism is increased (+); *red arrows* indicated where the energy metabolism is decreased (−)

resulting glucocorticoids release sustains this vicious cycle and may cause (i) the cortical and hippocampal atrophy and (ii) the monoamine depletion as an adapting response. In fact, both the *locus coeruleus* and dorsal *raphe*, i.e. the major sites within the CNS of NA and 5-HT synthesis, respectively, are enriched of glucocorticoid receptors as well.

Also metabotropic glutamate receptors have been implicated in mechanisms of resilience or non-resilience to stress, the latter being a hallmark of MDD, with particular highlight on the anatomical organisation of the dorsal raphe (containing 5-HT interneurons of the wings regulating the activity of projection neurons) and on the 5-HTTLPR S/L polymorphism, i.e. the 5-HTT-linked polymorphic region in the 5-HT transporter gene (SLC6A4) [177].

In particular, increasing evidence from both animal studies [178] and human neuroimaging studies [179] suggests that genetic variation in the 5-HT system affects the stress response and risk of depression through the critical brain circuitry underlying stressor reactivity and the regulation of emotion, which encompasses the amygdala, the ventromedial prefrontal cortex and the dorsal raphe nucleus [180]. The mechanistic hypothesis is that genetically produced variability in 5-HT reuptake during stressor-induced raphe–raphe interactions alters the balance in the amygdala–ventromedial prefrontal cortex–dorsal raphe nucleus circuitry underlying stressor reactivity and emotion regulation [177], involving 5-HT and, over time, the activity-dependent synaptic plasticity at the glutamatergic synapses in the amygdala [181].

By the way, drugs interacting with mGlu2 and mGlu5 receptors are under clinical development for the treatment of major depression. For example, several clinical studies evaluated L-acetyl-carnitine (LAC) antidepressant action in elderly MDD patients [92, 182] and a great attention has recently been put on LAC ability to modulate neuronal plasticity as donor of acetyl groups to proteins. In particular, LAC upregulates mGlu2 expression through the activation of the NF-κB pathway by p65 acetylation and through histone acetylation of mGlu2 promoter gene [183, 184]. Moreover, in rodent models of depression, LAC caused (i) a rapid antidepressant-like effect selectively associated with the enhancement of mGlu2 receptors in hippocampus and prefrontal cortex and (ii) the restoration of hippocampal depolarization-evoked glutamate release [184].

Remarkably, LAC is long known to be involved in brain energy metabolism through the increase of mitochondrial oxygen utilisation, slowing pyruvate flux to lactate [185–187] and buffering the acetyl-CoA pool [188]. Recently, LAC has been proven to have effects also on the ATP-ase energy-consuming systems, in particular on Na^+, K^+ and ATP-ase activity that was differently modified by LAC in rat frontal cerebral cortex [189], striatum [190] and hippocampus [191], being increased in this latter region. Since a reduction in this enzyme expression and function was associated with depression in humans [192, 193], again the concept appears that some alterations in proper energy production and consumption occur in mood disorders.

Overall, even if this hypothesis has to be validated, its merit is to draw the attention to the brain energy metabolism abnormalities in depression as potential pharmacological target. In fact, the above-reported adatpive processes, especially those involving de novo protein synthesis (e.g. the synthesis of enzymes, neurogenesis) and phosphorylation, closely depend on energy metabolism, requiring even considerable amounts of ATP. In the context of depressive disorders and correlated treatment paradigms, energy is of paramount important because numerous molecules of ATP are needed for G protein functioning, cAMP formation, PI resynthesis, protein kinase activities, various events at the synapse (transport of ions and neurotransmitter uptake) and protein synthesis. This last process is fundamental to the mechanism of antidepressants, whose action is related to changes in the levels and catalytic activities of various enzymes and, possibly, neurotrophic factors and neurogenesis [17]. Energy can thus be considered as the common denominator of all the aethiopathological theories for depression discussed so far.

This is evident considering that one molecule of ATP, corresponding to a $\Delta G = -7.5$ kcal/mol, is required for the formation of a peptide bond. Thus, the synthesis of a protein of n amino acids requires the consumption of $n - 1$ molecules of ATP, just to activate each amino acid. If, for example, n is equal to ≈1100–1200 (as in the case of AC and PLC), the synthesis of every molecule of these enzymes consumes a large amount of ATP [17]. Therefore, any changes caused by pathological conditions or pharmacological treatments will affect the biochemical events regulating ATP synthesis and metabolism, even more so when both second messenger systems are involved.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that there are no conflicts of interest.

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