WHAT DOES NEUROPLASTICITY TEACH US ABOUT TREATMENT-RESISTANT DEPRESSION?

Wolfgang P. Kaschka, Martin Jandl, Jürgen Steyer, and Steve Hodgkinson

University of Ulm, Department of Psychiatry I, Zentrum für Psychiatrie Südwürttemberg, Weingartshofer Strasse 2, D-88214 Ravensburg.

In recent years, developments in the field of treatment-resistant depression have not only brought about improved definition and classification, but also have led to an increase in our knowledge regarding the etiology and determinants of treatment resistance. A number of novel treatment strategies have been suggested which require critical evaluation before they are integrated into an evidence-based therapeutic concept. The present contribution provides an overview of these developments and reveals promising research perspectives which will extend our knowledge of the etiology and pathogenesis of depressive disorders and may thereby lead to the development of innovative therapeutic strategies for treatment-resistant depression.

Up to now, therapeutic concepts in treatment-resistant depression have mainly concentrated on the restitution of neurotransmitter balance between monoaminergic and cholinergic systems. But a number of factors have been neglected, some of which I will address here.

Several lines of evidence implicate dopamine in the pathogenesis and treatment of depression. First, there are consistent findings which point to decreased dopamine neurotransmission in depressed patients. Levels of homovanillic acid, the major metabolite of dopamine, have been shown to be reduced in the cerebrospinal fluid of depressed patients. A second line of evidence comes from studies of brain dopaminergic pathways. The mesolimbic and mesocortical pathways have been termed the ‚brain reward system' and this system appears to be affected by major depressive episodes.

Pharmacological experiments in rodents, suggest that antidepressant drugs of different classes and possibly also electroconvulsive treatment, increase the binding potential of dopamine D2-like agonists in the nucleus accumbens. This supersensitivity to dopamine has behavioural effects and might mediate at least some of the antidepressant properties of these somatic antidepressant treatments.

In the serotonergic system, S-adenosyl methionine (SAME) augmentation has been shown to be an effective adjunctive treatment strategy (Papakostas et al., 2010).

Guillin and coworkers (2001, 2003) reported from animal experiments, that in the hippocampus, some cortical areas, and possibly the ventral tegmental area, both serotonergic and noradrenergic antidepressant drugs increase Cyclic AMP response element binding protein (CREB) phosphorylation as well as probably other pathways. This activated CREB drives Brain-derived neurotrophic factor (BDNF) expression. BDNF has been shown to activate dopamine D3 receptor expression in the nucleus accumbens. As D2 and D3 receptors belong to the same receptor family, D2-like receptor agonists might be particularly effective as an augmentation to traditional antidepressant drugs.

Glutamate receptor stimulation is involved in processes of learning and memory, as well as in other plastic changes in the CNS such as synapse induction and elimination during development. On the other hand, glutamatergic dysfunction is characterized by excessive accumulation of extracellular glutamate, which, if not efficiently removed from the synaptic cleft by glutamate transporters, leads to excitotoxic neuronal cell death due to the overactivation of postsynaptic glutamate receptors. The three major mechanisms of the glutamatergic system that can be targeted pharmacologically are the presynaptic glutamate release

E-Mail: wolfgang.kaschka@zfp-zentrum.de

mechanisms, postsynaptic glutamate receptor activation, and the glutamate uptake mechanisms (Krystal, 2010; Li et al., 2010). For depression, amantadine, a nonselective NMDA receptor antagonist, has been shown to enhance the antidepressant-like effects of typical antidepressants in animal models (Rogoz et al. 2002, 2004). In addition, AMPA receptor agonists are proposed to augment typical antidepressant effects in animal models (Li et al. 2003; Pilc et al. 2002).

A number of drugs are available that target presynaptic glutamate release. Riluzole is an antiglutamatergic agent that is believed to reduce extra-synaptic glutamate levels by decreasing presynaptic glutamate release. Riluzole, which has been successfully used in amyotrophic lateral sclerosis (ALS) patients (Miller et al. 2003; Rivière et al. 1998), has demonstrated its efficacy in monotherapy in treatment-resistant major depression as well as an augmenting agent in bipolar depression (Zarate et al, 2004, 2005). Similarly, lamotrigine, also a drug believed to reduce presynaptic glutamate release, has been shown to be effective in the treatment of bipolar depression when used as monotherapy or as an augmentation agent. These studies lend support to the value of investigating antiglutamatergic drugs as an approach to the management of treatment-resistant depression. Recent studies suggest that increasing glutamate uptake offers yet another new therapeutic target for neuroprotection against excessive neurotoxic levels of extracellular glutamate (Salvadore and Zarate, 2010).

Chronic lithium treatment increases the uptake of glutamate and also can reduce the increase in intracellular calcium that occurs as a result of NMDA receptor activation. These actions may provide mechanisms for lithium to reduce excitatory neurotransmission and contribute to lithium‘s neuroprotective effects against certain excitatory insults.

The term “neuroplasticity“ subsumes diverse processes of vital importance by which the brain perceives, adapts to and responds to a variety of internal and external stimuli. The manifestations of neuroplasticity in the adult CNS have been characterized as including alterations of dendritic function, synaptic remodeling, long-term potentiation (LTP), axonaI sprouting, neurite extension, synaptogenesis, and even neurogenesis.

It has recently been proposed that impairments of neuroplasticity and cellular resilience may underlie the pathophysiology of mood disorders (Manji et al., 2000), and further that optimal long-term treatment for these severe illnesses may only be achieved by the early and aggressive use of agents with neurotrophic and/or neuroprotective effects, alongside the primary, symptomatic treatments. Such treatment modalities, via their effects on critical molecules involved in cell survival and cell death pathways, such as CREB, BDNF, Bcl-2, p53 and MAP kinases, have the potential to enhance neuroplasticity and cellular resilience, and thereby modulate the long-term course and trajectory of these devastating illnesses.

Genetic and neurodevelopmental factors, repeated affective episodes and likely elevations of glucocorticoids and illness progression may all contribute to the impairments of cellular resilience, volumetric reductions, and cell death or atrophy observed in mood disorders. Bcl-2 attenuates apoptosis by sequestering proforms of death-driving cysteine proteases (called caspases), by preventing the release of mitochondrial apoptogenic factors, such as calcium, cytochrome C and apoptosis-inducing factor, AIF, into the cytoplasm, and by enhancing mitochondrial calcium uptake. Moreover, Bcl-2 acts on mitochondria to stabilize membrane integrity and to prevent opening of the permeability transition pore.

Lithium, via its effects on Bcl-2 and p53, may exert effects on the mitochondrial permeability transition pore, a key event in cell death. Lithium and valproic acid also inhibit GSK-3β, a biochemical effect shown to have neuroprotective consequences (Jope and Bijur, 2002; O`Brien and Klein, 2007). Valproic acid also activates the ERK MAP kinase pathway, which may play a major role in neurotrophic effects and neurite outgrowth. The ERK MAP kinase cascade also increases the expression of Bcl-2 via its effects on CREB. Antidepressants regulate the expression of BDNF, and its receptor, tyrosine kinase receptor for BDNF (trk B; Duman et al., 2007).

With regard to glial cells, there is a growing appreciation of the critical roles of glia in regulating synaptic glutamate levels, CNS energy homeostasis, liberation of trophic factors, and indeed the very existence of synaptic networks of neurons and glia, all of which suggest that the prominent glia loss observed in major depressive disorder and bipolar disorder may be

integral to the pathophysiology of these disorders, and therefore worthy of further study.

Further lines of research have been suggested in the field of affective disorders during recent years (Krishnan and Nestler, 2010; Holsboer, 2010), among them functional genetic variation of neuropeptide Y (Mickey et al., 2011), the role of proteomics (Martins – de Souza et al., 2010), and – finally – the development of personalized medicine (Bartova et al, 2010; Schwab et al., 2010).

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