A New Paradigm to Indicate Antidepressant Treatments

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This entry describes that a new paradigm must be applied in which the relative value of antidepressant treatment is specifically weighted in terms of enabling the natural resilience process.

Keywords: depression

1. No Evidence for Specific ('True') and Nonspecific Antidepressant Drug Response

Recently, research about possible associations between the responses to antidepressant treatment and specific pharmacogenes in over 150 antidepressant-free patients with depression [1][2]. These newly admitted patients had not been treated with antidepressant drugs during the preceding six months and 54.5% had never been treated with antidepressant drugs during their entire life. They had a clinical diagnosis of depression according to ICD-10 criteria [3] of at least moderate severity, as measured by Hamilton's depression rating scale (HAMD-17) [4][5], and were studied over four weeks. According to the old but still very influential theory of Quitkin et al. [6], activation of the 'true' antidepressant mechanism takes 2–4 weeks to occur after antidepressant therapy starts, the initial treatment response being comparable with that of the placebo, hence nonspecific or spontaneous. The existence of such a lag time indicates that the acute pharmacological effects occurring after a short time result in activation of a unified mechanism that alleviates the complete syndrome. With this theory in mind, we compared the response during the first two weeks with that during the last two weeks. For the total group, the average HAMD-17 score amounted to 24.3 ± 5.2 (mean ± standard deviation) at entry, and this decreased to 12.9 ± 4.9 and 5.0 ± 3.9 after treatment at two weeks and four weeks, respectively [1]. Obviously, in this study, there was no question of perceiving a delayed response of two to four weeks for the antidepressants to show an effect in the depressed patients. The indication of the existence of such a 'lag time' through clinical experience has been debated by several authors when considering the course of the response over time in different patient groups in meta-analysis of controlled clinical trials [7]. The results of the research group of the Zürich Psychiatric University Hospital are particularly convincing in this respect [7]. These authors studied the individual pattern of improvement in 2848 patients with MDD who had participated in four independent clinical trials using a total of seven different antidepressants and a placebo. They found that the period to the onset of improvement (the latency time) and the pattern of improvement did not differ between the verum treatment and the placebo; however, the number of responders (incidence of improvement) was higher with verum than with the placebo. The fact that the early and large response in Ochi et al.'s study [1] was related to a placebo effect (a spontaneous resilience mechanism) was contradicted by the results of another study on the same population by our research group, which investigated the influence of polymorphisms of the gene encoding for P-glycoprotein (*ABCB1*) on the timing of the observed improvement [2]. Certain genotypes caused a partial shift in the improvement during the first two weeks compared to the second two weeks of treatment. This indicates that a pharmacological effect may at least contribute to the improvement in the clinical condition. The transporter P-glycoprotein limits the passage of antidepressants through the blood–brain barrier, and certain genetic variants may influence the rapidity and intensity with which CNS structures are pharmacologically affected by antidepressants. Of note, Stassen et al. [7] suggested that antidepressants activate 'a common, biological, 'resilience'-like component that largely controls recovery from depression'.

2. A Theory of the Background Biopsychosocial Components

Theory of knowledge teaches that scientific endeavor needs a model: a simplified representation of reality along the lines of a certain theory, suitable to effectively create a hypothesis that can be experimentally falsified or preliminarily confirmed. A fruitful method to combine the relevant neurochemical and neuroanatomical components into a single theory involves simplifying these structures of the central nervous system according to their evolutionary genesis. In line with this proposal, we developed a model as shown in **Figure 1**. Here, the primary forebrain, which regulates the essential behaviors associated with feeding, defending, and reproducing, was already present in the very first vertebrates (living

560 million years ago (mya)) and is represented in humans by the amygdaloid and hippocampal complexes and the hypothalamus. The secondary forebrain was already found in early amphibians (living 370 mya), and in humans, it consists of limbic ventral extrapyramidal circuits that regulate that willingness and intensity of these essential behaviors. The activity of the primary and secondary forebrain is regulated by ascending dopaminergic, serotonergic, and adrenergic pathways from the midbrain, which, in turn, are controlled by the dorsal diencephalic connection system (habenula).

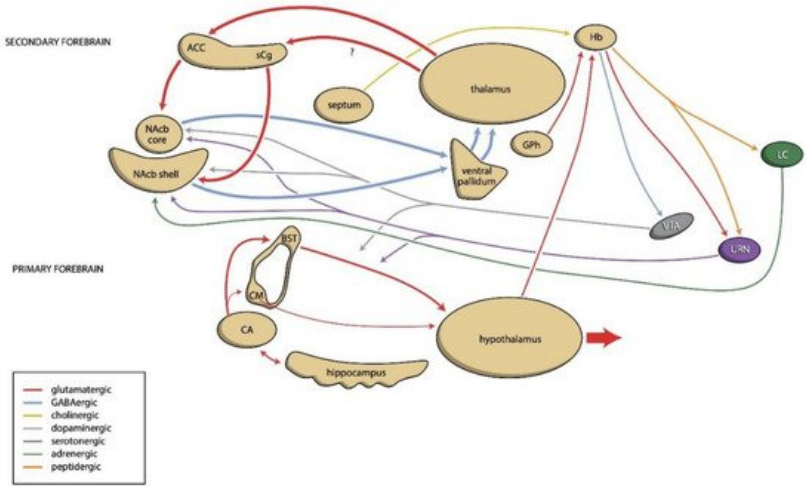

Figure 1. Hypothetical model representing the connectivity of the human primary and secondary forebrain. Our hypothesis suggests that the emotional response is initiated by the amygdalo-hippocampal complex and executed by the hypothalamus. The intensity of reward-seeking and distress-avoiding behavior is regulated by two parallel sets of cortical-striatal-thalamic-cortical (CSTC) circuits within the secondary forebrain, which include the nucleus accumbens (ventral striatum). The habenula controls the activity of these circuits by affecting ascending monoaminergic neuronal pathways. For further substantiation of this model, see Loonen and Ivanova [8][9]. ACC—anterior cingulate cortex; BST—bed nucleus of the stria terminalis; CA—corticoid part of the amygdala; sCG—subgenual cingulate cortex; CM—centromedial nucleus of the amygdala; GPh—the human equivalent of the habenula-projecting part of the globus pallidus; LC—locus coeruleus; Hb—habenula; NAcb—nucleus accumbens; URN—upper raphe nuclei; VTA—ventral tegmental area; CM and BST—extended amygdala.

By integrating physiological and pharmacological information with this anatomical model, we came up with the idea of the existence of two sets of limbic extrapyramidal re-entry circuits (see **Figure 1**) that partially independently drive the intensity of reward-seeking or distress-avoiding behavior, which, when successful, result in pleasure or happiness, respectively. This corresponds to the existence of two interrelated components of depressive disorders: one regulating the energy level and appetitive motivation and the other related to worrying and feelings of hopelessness. This results in a theoretical model where primary parts of the forebrain still initiate the emotional response when an opportunity occurs to obtain food, or to mate, or when safety is endangered. The secondary part of the forebrain, which regulates the readiness to, and the intensity of, the generated emotional response, is probably directly involved in addiction and bipolar disorder, as well as in depressive disorders. This model can also be applied to explain the rapid antidepressant effect of (es)ketamine. This substance probably acts on the habenula, regulating the activity of the ascending monoaminergic pathways from the midbrain.

The application of this model could be useful in defining psychopharmacological effects with a potential benefit in patients with mood disorders. Mood disorders are probably best considered to consist of a variable set of regulatory dysfunctions, which are neither unique for a specific type of mood disorder, nor essential for any one of them. Such dysfunctions could be defined within the context of the model to identify possible goals of treatment. Effective treatments of the largest disease-contributing dysfunctions may already enable natural resilience mechanisms to induce further (partial or complete) recovery. Therefore, once essential contributing biological factors allow for it, the sociocultural mechanisms can sufficiently motivate the individual to abandon depressive behavior. As the effect of natural resilience mechanisms, which also occur when the individual is treated with a placebo [7], is minimalized in pharma-trials, the effectiveness of antidepressant drugs is probably artificially lowered.

3. The Backgrounds of the Resilience Component

In addition to the above biological evolution that took more than 500 million years, humans also culturally evolved during fewer than the last 50,000 years [10]. Essential to the development of human culture and technology was the acquisition of writing skills. Writing enabled humans to communicate without direct physical contact, which thereby facilitated

developments that built on the ideas of others. This skill has also played a major role in developing our thinking about having depression. Throughout about three millennia, the opinions of the consecutive writers on the symptomatology and impact on quality of life concerning mood disorders have been largely preserved. This facilitates the portrayal of the concept of depression as not being a recent psychiatric discovery, but as part of human history. The writings of ancient Israelian prophets [11] and Greek philosophers [12] still partly determine our views concerning mental illnesses. Their viewpoints were included in medieval Christian writings, where certain depressive states were also considered a mortal sin, particularly by Gregory the Great (Pope 590–604 AD) [13]. The influence of Genghis Khan (1162–1227AD), who expanded his Mongol Empire across Eurasia, thus allowing the views of Chinese, Indian, and Persian natural philosophers to be freely exchanged, should also be considered, especially in the more eastern parts of Europe [14]. 'His empire eventually encompassed all or part of modern China, Mongolia, Russia, Ukraine, Korea, Azerbaijan, Armenia, Georgia, Iraq, Iran, Kazakhstan, Kyrgyzstan, Uzbekistan, Tajikistan, Afghanistan, Turkmenistan, Moldova, Kuwait, Poland, and Hungary' [14]. The religious beliefs that found their basis in medieval thought eventually determined the type of madness that nineteenth-century brain psychiatrists engaged with [15]. This undeniably also applies to the disease categories described by Emil Kraepelin [16]. He began by studying the syndromes in patients in Estonian psychiatric asylums [17][18]. This means that he excluded many mentally disturbed patients who were considered more sinful or bad than mad, and/or when they belonged to the higher social classes. The same is probably true for other nineteenth-century psychiatrists [19][17][18][20]. In addition, Kraepelin himself did not speak Estonian [21] and his findings were colored even further by the pre-scientific views of the interpreters involved. The main point we want to make is that leading psychiatrists of the nineteenth and early twentieth centuries did not escape from the dominant religious beliefs of their societies that considered that depression could be madness as well as sinful/bad behavior or character weakness. They excluded several mood disorders from consideration because these were considered to belong to the religious and/or juridical domain; in that sense, their selection was also based on the prejudices fed by historical writings and popular pre-scientific beliefs about psychiatric illnesses. However, this has been ignored by late twentieth-century psychiatrists, who have 'atheoretically' included these depressive human problems without restrictions in the final MDD disease categories of the DSM-5 [22] and ICD-11 [23].

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