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Future Directions for Serotonin and Antidepressants

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Despite the widespread use of antidepressant medications that block serotonin (5 hydroxytryptamine; 5-HT) and/or norepinephrine (NE) transporters, such as SSRIs (selective serotonin reuptake inhibitors) or SNRIs (serotonin and norepinephrine reuptake inhibitors) (Fig. 1), the underlying neurobiological basis of action of these agents is poorly understood. Increases in serotonergic function are hypothesized to have beneficial effects on depressive symptoms. However, which of the 14 different neuronal receptors sensitive to 5-HT accounts for the therapeutic effects of SSRIs and SNRIs remains undetermined. The development of drugs that activate or block specific 5-HT receptors may help to circumvent the two main limitations of current antidepressants: low efficacy and delayed onset of therapeutic action. What follows is a short summary of the authorsø views on this matter.

Major depression is a severe psychiatric syndrome with a lifetime prevalence of 10% and 20% for men and women, respectively, and high socioeconomic impact [1]. Unfortunately, the increasing cost of depression and related affective disorders has not been paralleled by improvements in the efficacy of antidepressant treatment. SSRIs and SNRIs are pharmacological refinements of the first generation of antidepressant drugs ï tricyclic drugs such as imipramine or chlorimipramine ï discovered serendipitously while searching for new antipsychotic drugs with a chemical structure similar to that of chlorpromazine (Fig. 1). In addition to blocking monoamine reuptake, tricyclic antidepressants exhibit high affinity for a number of neurotransmitter receptors ($Ŭ_1$-adrenoceptors, histamine H1, muscarininc receptors, etc.). The interaction of tricyclic drugs with these receptors is responsible for their adverse side effects (postural hypotension, dry mouth, blurred vision, constipation, memory or cognitive impairment, etc.), which force many patients to abandon treatment with these drugs. The synthesis of new molecules inhibiting monoamine reuptake, devoid of these additional pharmacological activities, fostered the development of a new era in the treatment of major depression and other psychiatric diseases. The SSRIs ï and later, the SNRIs ï allowed patients to comply with therapeutic regimes, thereby increasing the overall numbers of patients experiencing antidepressant effects.

However, despite increased compliance, the efficacy of SSRIs did not surpass that of some tricyclic drugs, such as clomipramine [2,3]. Clinical trials with selected patient populations typically indicated response and remission rates of 60% and 40%, respectively, with SSRIs [4,5]. However, naturalistic studies, such as the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial revealed a less promising situation, with response and remission rates of ~50% and a ~30%, respectively, after treatment with the SSRI S-citalopram (Fig. 1). Augmentation strategies with drugs not targeting the serotonin transporter (SERT) in patients

not responding to SSRIs yielded similar remission rates, around 30% [6]. Thus, these ñreal worldò figures indicate that a very large percentage of patients treated with SSRIs show partial responses, leaving much room for improvement in antidepressant treatment.

The last two decades have witnessed major advances in our knowledge of glutamatergic transmission. In addition to direct excitatory activity mediated by ionotropic receptors (AMPA, NMDA, KA), glutamate can exert modulatory actions, similar to those of monoamines, via the activation of three families of metabotropic receptors, with a total of 8 different receptors identified (mGluR1-mGluR8), which offer potentially new avenues for neuropsychiatric drug development. For example, an mGluR2/3 agonist is being developed for the treatment of schizophrenia [7]. This is the first antipsychotic drug devoid of affinity for dopamine receptors illustrating the potential of mGluRs in drug development. Moreover, the non-competitive NMDA antagonist ketamine can evoke rapid (~2 h) and persistent (up to 1 wk) antidepressant effects after a single dose in treatment-resistant depressed patients [8]. Interestingly, the dose used in antidepressant clinical trials of ketamine is the same as that displaying psychotomimetic effects. Overall, this suggests that the glutamatergic system may offer excellent opportunities for the development of antidepressant drugs overcoming the limitations of SSRIs and SNRIs. Yet, despite these promising results, the development of glutamatergic antidepressants may be hampered or delayed for several reasons, described briefly below.

With the exception of the basal ganglia ï where GABA is the principle neurotransmitter ï the basic wiring of the brain comprises excitatory glutamatergic neurons. This raises the possibility that glutamatergic drugs will elicit new and unexpected side effects, different from those of SSRIs or SNRIs, given the distinct roles played by glutamate and the monoamines in brain function. In addition to efficacy, the safety of new glutamatergic drugs will be a major issue that will require testing in large numbers of patients for long periods of time in phase IV clinical trials. Further, at the time of writing, CNS drug development is being abandoned or reduced by several large pharmaceutical companies, thus reducing overall research and development aimed identifying new targets and novel therapeutics. Thus, it is likely that antidepressant drug development in upcoming years will not broaden beyond monoaminergic systems. Monoaminergic drugs offer advantages associated with >50 years of clinical experience, with millions of patients treated, and a relatively good knowledge of their side effects.

As stated above, a major problem of SSRIs and SNRIs is their poor efficacy and slow clinical action. With an almost saturated antidepressant market, new drugs should be faster and/or more efficacious than SSRIs and SNRIs to achieve success. These new developments must be based on the knowledge of the role played by the different 5-HT receptors in

depression, a highly complex field, given the existence of 14 different 5-HT receptors, different localizations in brain networks, and sometimes opposing actions on neuronal activity after stimulation by 5-HT. Presynaptic 5-HT_{1A} and 5-HT_{1B} autoreceptors are suspected of playing a major detrimental role in current antidepressant therapy due to activation of negative feedback mechanisms operating in 5-HT neurons [9, 10]. Conversely, activation of postsynaptic 5-HT_{1A} receptors in corticolimbic networks has positive antidepressant action [11,12]. This paradoxical situation may perhaps be solved by small-interferring RNA (siRNA) mechanisms selectively targeting pre- or postsynaptic receptors [13] or by the development of agonists selective for postsynaptic 5-HT_{1A} receptors [14,15]. On the other hand, blockade of 5-$HT_{2A/2C}$ receptors improves the actions of SSRIs, whereas 5-HT_{2B} receptor activation enhances serotonergic activity and shows antidepressant-like activity in rodents [16]. 5-HT_3 receptor blockade can also augment the antidepressant action of SERT inhibition, whereas 5-HT_4 receptor activation has antidepressant effects on its own and augments SSRI effects [17]. Finally, blockade of 5-HT_6 and 5-HT_7 receptors may also improve the antidepressant effects of SERT inhibition (very little is known about the role of 5-HT_5 receptors) [18,19]. Given the poor capabilities to model depressive symptoms in animals, it is unclear whether these different serotonin receptor pharmacologies have selective actions on particular groups of symptoms (*e.g.*, affective, cognitive, somatic, etc.) or affect a range of symptoms, similar to SSRIs and SNRIs.

These observations indicate that the activation of the various 5-HT receptors by SSRI and SNRI has opposing effects on the activity of brain networks underlying their therapeutic effects. Therefore, it would be advisable to design antidepressant drugs encompassing agonist and antagonist activities at most relevant 5-HT receptors, an objective likely unfeasible from a chemical point of view. On the other hand, it is uncertain whether the selective activation of a single 5-HT receptor subtype is able to elicit antidepressant effects superior to those of current drugs. Therefore, future antidepressant strategies might include combinations of SERT blockade plus some of the above activities, an approach initiated by recently developed antidepressant drugs (e.g., vilazodone or Lu AA21004, also known as vortioxetine; Fig. 1). In addition to blocking SERT, both drugs incorporate partial agonist activity at 5-HT_{1A} receptors. Also, vortioxetine shows antagonist activity at 5-HT_3, 5-HT_{1B}, and 5-HT_7 receptors. Both drugs elevate extracellular 5-HT to a great extent compared to SSRIs, possibly by overcoming negative feed-back mechanisms that limit the full effect of SERT blockade [20,21]. Future serotonergic drugs may also include other targets potentially useful for antidepressant activity, such as blockade of 5-$HT_{2A/2C}$ receptors or activation of 5-HT_4 receptors. Likewise, further clarification of brain elements (neurotransmitters, receptors, cells, networks) responsible for the

therapeutic effects of antidepressant drugs will guide the development of new generations of antidepressants overcoming the important limitations of current drugs.

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Conflict of interest

F. Artigas has received lecture fees from Eli Lilly and Lunbeck A/S and consultancy fees from Lundbeck A/S on the mechanism of action of antidepressant drugs.

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Figure legend

Figure 1. Structures of psychoactive drugs. Chlorpromazine is an antipsychotic that served as the framework for the discoveries of imipramine and clomipramine, tricyclic monoamine reuptake inhibiting antidepressants having multiple off-target effects that limit usage. Based on the efficacy of the tricyclics, newer antidepressants have been developed that selectively inhibit serotonin reuptake (SSRIs; fluoxetine, paroxetine, S-citalopram) or are dual serotonin-norepinephrine uptake inhibitors (SNRIs; duloxetine, venlafaxine). New antidepressant drugs that inhibit serotonin reuptake and have added action as partial 5-HT_{1A} agonists have recently been developed: vilazodone (EMD 68843) and vortioxetine (LuAA21004). The latter drug shows additional affinity for other 5-HT receptors (see text).