FORUM Depression

The best way forward

Conventional behavioural mouse models of depression are often used to study the disorder, but cannot capture the full picture of the human disease. Here, scientists present two views about the best research strategies to adopt if treatments are to be improved.

THE TOPIC IN BRIEF

- Depression is one of the most prevalent disorders of mental health.
- The development of drugs to treat depression has been stalled for decades.
- Some think that a biological understanding of the mechanisms by which known, rapidly acting antidepressants exert their effects will facilitate the development of improved treatments.
- Others believe that elucidating the neuronal circuits that mediate the symptoms of depression is paramount if the field is to move forward.

Put therapies first

LISA M. MONTEGGIA

Current antidepressant medications work by increasing the levels of monoamine neurotransmitter molecules at synapses (the junctions between neurons across which chemical signals are transmitted). Although monoamine levels change quickly once treatment with antidepressants starts, the drugs typically take several weeks to exert a clinical effect. Moreover, although they are effective in some patients, in others — notably, those most at risk of suicide — there is often no response. This emphasizes the pressing need to develop rapidly acting antidepressant medications with limited side effects. Many researchers are trying to do this by modelling depression-like characteristics in animals, with the aim of identifying the neuronal circuits underlying the disorder. However, I believe that a better way to design improved drugs is to elucidate the biological mechanisms that underpin effective, rapidly acting antidepressants.

Studies of depression using animals largely focus either on behavioural tests such as stress responses, or on attempts to model and measure aspects of the disorder, such as helplessness or anhedonia (the inability to experience pleasure). Rodents that show intrinsic depression-like behaviour are also studied[1]. These models should be treated with caution[2], because it is unclear how well they correspond to the human behaviours they are purported to replicate. Nonetheless, their use has been undeniably valuable for developing a constructive debate about the abnormal changes in physiology (the pathophysiology) that lead to depression and, by extension, about treatment options.

But despite the positive aspects of animal models, the most direct route to improving treatments — understanding the biology underpinning therapies that have some success in humans — is surely the best way forward. This approach has proved successful in drug-addiction studies. These have focused on the biological action of cocaine, yielding insights not only into potential therapies but also into the neuronal circuits that underlie addiction. But it is difficult to determine how classical antidepressants work because of the time it takes for the drugs to exert their effects. The discovery that acute, low-dose ketamine triggers a rapid antidepressant response[3], even in patients categorized as treatment-resistant[4], provides a golden opportunity to better delineate the pathways involved in antidepressant action.

Since the clinical observations regarding ketamine were made[3,4], their underlying biological mechanisms have been teased apart in animals in the laboratory — an approach known as reverse translation (Fig. 1a). This has led to the identification[5] of ketamine's target (a receptor protein for the neurotransmitter molecule glutamate) and to the finding that blockade of this receptor by ketamine is linked to changes in a specific signalling pathway. These changes may result in the increase in synaptic efficiency that underlies the drug's rapid effects[6].

Such findings move us closer to understanding how ketamine acts, and may help to identify drugs that work in similar ways. In particular, the knowledge gleaned from this reverse-translation approach indicates that an antidepressant response can be triggered in a manner distinct from those of classical antidepressant drugs. The discovery finally moves the field beyond the old focus on increasing synaptic monoamine levels[6].

There are clear problems with using animals to model neuropsychiatric disorders, because such conditions are probably caused by a variety of factors. But if the biological basis is to be understood, animal models will obviously be required to examine the genetic variants and genetically linked characteristics associated with complex disorders such as depression. However, no animal model will ever fully correspond to this devastating human condition. Therefore, such efforts must be combined with the investigation of promising pharmacological leads in humans if improved treatments are at last to be found.

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Fix faulty circuits

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Drugs to treat psychiatric disorders such as depression were discovered serendipitously in the 1950s, concomitant with the realization that drugs can also cause syndromes resembling mental illness[7]. The ensuing decades saw attempts to identify the molecular targets of antidepressants and the evolution of simple biochemical models of mental illness. Such pharmacological approaches have provided minimal insight into the

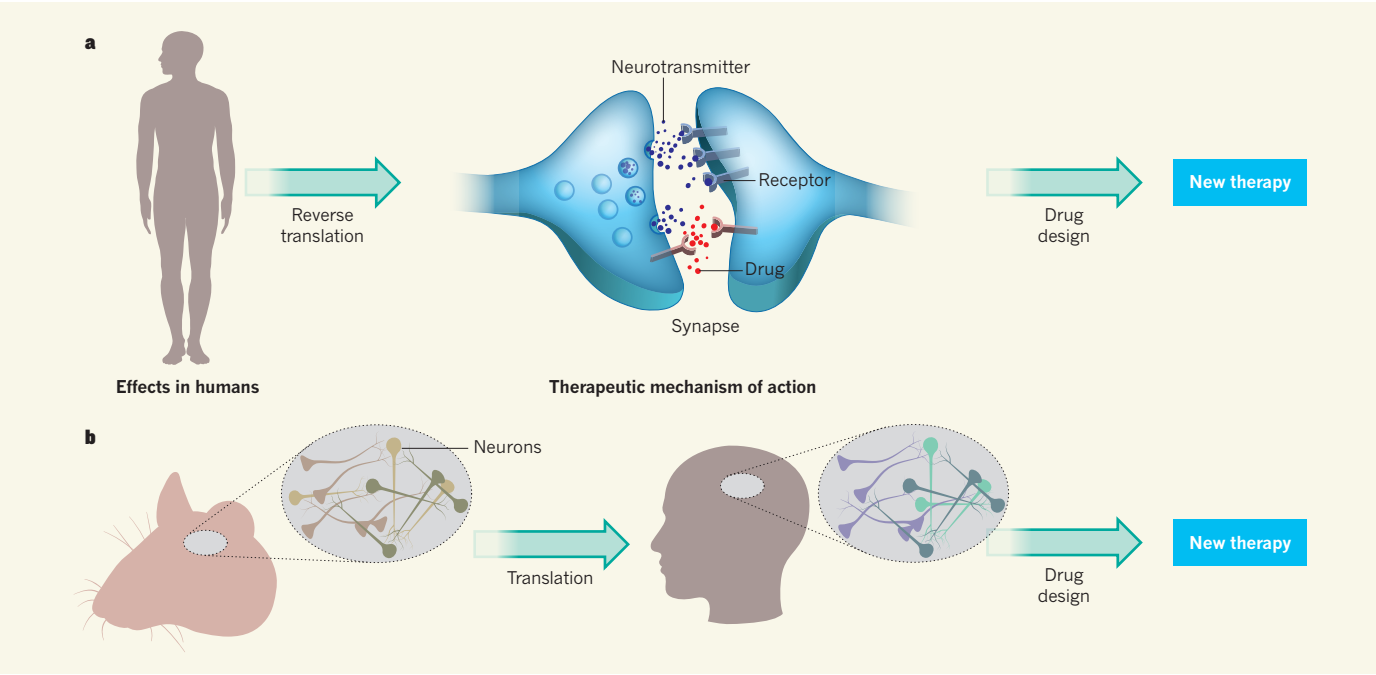

Figure 1 | Approaches to drug discovery for depression. There is a consensus among researchers that successful drug development will require a concerted effort, embracing approaches based on both pharmacology and neuronal circuits. However, there is debate about where such an effort should focus first. **a**, Antidepressants that are effective in humans can be reverse translated in the laboratory, to infer how treatments can be improved. The mechanisms of action of effective drugs are teased apart, to give a biochemical understanding of how an antidepressant such as ketamine exerts its effects at synapses, the neuronal junctions across which neurotransmitter molecules are passed. This knowledge can then be used to identify new targets for treatment or to develop more-effective drugs that act on known targets. **b**, An alternative approach is to dissect the neuronal circuitry that malfunctions in animals showing symptoms of depression. Once a dysfunctional circuit has been identified, the same circuit can be analysed in humans. In this way, putative drug targets can be defined and tested in a reliable animal model, and then eventually tested in humans.

pathophysiology of mental illness, and have led only to the development of drugs that have similar biochemical actions to those of their predecessors, rather than improved efficacy[7]. However, this strategy is still commonly taken by both academics and pharmaceutical companies. We believe that a sophisticated understanding of the pathophysiology of mental illness at the level of neuronal circuits provides a more rational way forward.

A prototypical example of the pharmacological approach is a model of schizophrenia based on administering ketamine to animals and humans[8]. It could be argued that studying how ketamine acts will not only help us to understand schizophrenia better, but might also provide clues to treating depression, because it is an effective short-term treatment for this disorder. Although we welcome such pioneering clinical work, the decades-old history of psychiatry research indicates that attempts to define this drug's therapeutic mechanism of action are doomed to failure[7]. Those who cannot remember the past will almost certainly repeat it.

In its broad action, ketamine treatment is analogous to electroconvulsive therapy (ECT) and lithium. These are effective therapies for refractory depression and bipolar disorder, respectively, but, like ketamine, affect neurons indiscriminately throughout the brain. As a result, the many attempts to define the biological mechanisms by which ECT and lithium act have led neither to a better understanding of the changes in physiology that are responsible for disease nor to improved treatments.

The path to better treatments might more suitably lie in defining the specific brain circuits that mediate symptoms of mental illness. Improved methods for recording and manipulating neural activity have led to advances in defining the circuits that mediate several symptoms. For instance, in rodents, manipulation of key cells in the brain's reward circuitry has profound effects on anhedonia[9,10]. Similarly, circuits involving another area of the brain have been found to mediate features of anxiety, which often accompanies depression[9,10].

Although conventional animal models of psychiatric symptoms (which are based on pharmacology) have legitimately been called into question[2], advances in our understanding of the genetics of mental illness have facilitated the development of rodent models with strong construct validity — that is, behavioural abnormalities in the model are brought about by the genetic defects that cause disease in humans. These models provide ideal systems in which to dissect the circuitry that mediates maladaptive behaviours. Importantly, circuits found to be malfunctioning in animals can be tested in human brains using imaging and stimulation techniques (Fig. 1b). In this way, researchers are beginning to identify the circuit dysfunctions that cause key symptoms of mental illness[9–11].

This process may ultimately allow drug development to become rational. The aim is to identify targets in neuronal circuits that, when manipulated, can repair the dysfunction. After more than 50 years of stagnation, the field may be ready to move beyond the same pharmacological approaches and instead leverage more-suitable methods for advancing our understanding of the circuitry involved[11]. It is time to make history, not repeat it. ■

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