BRAIN CIRCUITS INVOLVED IN ANTIDEPRESSANT RESPONSE

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The pathophysiology and treatment of major depression are still controversial issues. Theories based on abnormalities of monoaminergic neurotransmitters have dominated the scene for about 4 decades, mainly due to the fact that most antidepressant treatments enhance serotonergic and noradrenergic function.1 The discovery that stress reduces synaptic contacts in the limbic system while antidepressant drugs increase the expression of genes related to synaptic plasticity, such as neurotrophic factors (particularly BDNF) and hippocampal neurogenesis led to propose a trophic action for antidepressant drugs. More recent views, however, have focused on the key role of certain cortical areas, such as the prefrontal cortex. Hence, deep brain stimulation of Broadman area 25, in the subgenual cingulated gyrus, was able to bring about a rapid and effective recovery in depressed patients refractory to antidepressant polipharmacy. This opened new perspectives, suggesting that major depression may be associated to the improper function of one or several brain circuits.

Indeed, depressive symptoms include anhedonia, depressed mood, cognitive impairment, fear and anxiety, feelings of guilt and worthlessness, sleep disturbances as well as somatic changes such as tiredness and motor impairment, which suggests the involvement of neuronal networks controlling a variety of brain functions. Actually, some of these symptoms can be associated to the improper function of one or more brain areas/networks. Hence, anhedonia and a poor recollection of pleasant memories can be linked to a malfunction of the ventral striatum and the associated mesolimbic dopamine pathway. Fear and anxiety can be associated to a hyperactive amygdala whereas cognitive impairment can be linked to an improper function of certain cortical areas. Moreover, somatic and sleep disturbances can result from hypothalamic abnormalities and an improper function of thalamocortical networks.

The brain is an extraordinary biological tool that integrates sensory information from the environment and combines it with a vast array of stored information to produce a single, yet extremely complex product: behavior. One of the crucial and still unresolved questions in Neuroscience is how behavior can emerge from the coordinated activity of billions of neurons distributed in many different brain areas. The prefrontal cortex (PFC) is a key cortical area exerting a top-down control of many brain networks. Automatic or stereotyped behaviors do not require its engagement of the prefrontal cortex (PFC). For instance, directing our attention to a spot where we hear a sudden noise is carried out by an innate connectivity between sensory and motor areas that does not involve the PFC. This type of behavior is carried out through “bottom-up” processing of sensory signals. In contrast, the PFC plays a key role in situations with a large number of degrees of freedom, i.e., when flexibility is required to behave in a novel, unexpected environment or when behavioral rules change. The PFC receives sensory information from the external world, stored emotional and contextual information from limbic and temporal areas, and has a large number of intrinsic connections between different subregions of the PFC itself.

Interestingly, the PFC exerts a tight, top-down control of monoaminergic systems putatively involved in major depression. Anatomical and functional studies have revealed that 1) the PFC projects to these brainstem nuclei, and 2) that activity changes of PFC projection pyramidal neurons result in immediate changes of the activity of monoaminergic systems, often with complex patterns. Hence, the physiological stimulation of PFC can excite or inhibit serotonergic neurons of the dorsal raphe. Complex patterns of activity in response to PFC stimulation have also been reported for noradrenergic and dopaminergic neurons. Thus, gene x environment alterations of PFC function can alter the activity of the ascending monoaminergic systems whereas antidepressant drugs can normalize their function through the blockade of the respective membrane transporters. On the other hand, the normalization of these reciprocal PFC-monoamine brain circuits can be achieved through the suppression/stimulation of the activity of certain PFC areas, as observed with highfrequency stimulation of Broadman area 25.

One key aspect in the required enhancement of monoaminergic function for depression treatment is the observation that antidepressant activate a physiological negative feed-back mechanism involving monoaminergic autoreceptors (5-HT1A and 5-HT1B in serotonergic neurons; α2-adrenoceptrs in noradrenergic neurons). The acute excess of serotonin or noradrenaline concentration in the extracellular fluid induced by reuptake or MAO inhibition activates these autoreceptors, reducing neuronal activity and monoamine release. Thus, full effects of antidepressant drugs occur only after autoreceptor desensitization, a time-course consistent with the 2-3 weeks of treatment required to observe clinically meaningful effects. These observations led us to propose the use of autoreceptor antagonists as potential enhancers of the clinical action of antidepressant drugs. The non-selective 5-HT1A (partial) antagonist pindolol has been used to accelerate and enhance the clinical effects of SSRIs. However, pindolol is a non-selective agent which also blocks ß-adrenoceptors. The development of 5-HT1A antagonists selective for 5-HT1A autoreceptors is hampered by their similar blockade of pre- and postsynaptic 5-HT1A receptors, which clearly limits their usefulness since activation of postsynaptic 5-HT1A receptors appears necessary for antidepressant effects of SRIs. Thus, our more recent studies have focused on the use of interference RNA technologies (siRNA; small interference RNA) in order to selectively knockdown presynaptic autoreceptors while preserving postsynaptic 5-HT1A receptor function. Pilot studies have revealed that the stereotaxic application of siRNA molecules directed towards 5-HT1A receptors in the dorsal raphe markedly reduced 5-HT1A receptor expression and function, and that this effect was associated with an antidepressant-like response in behavioural tests and with an enhancement of the increase of extracellular serotonin induced by the SSRI fluoxetine. Work is in progress to selectively deliver siRNA molecules to serotonergic neurons via systemic routes.