

ANIMAL MODELS OF DEPRESSION AND MECHANISM OF ACTION OF ANTIDEPRESSANTS: A CRITICAL PERSPECTIVE

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Over the course of the last 50 years many animal models of depression have been developed on the basis of pathogenetic theories on this disorder. These models in turn have been crucial for the search of new antidepressants. However, the “tautological” relationship between animal models, mechanism of action of antidepressants and clinical effectiveness does not always hold. Thus, discrepancies between positive outcomes of new candidate drugs in animal models and efficacy in humans have been numerous and have generated much concern over the predictive validity of current animal models of depression. These discrepancies in turn have impacted on research strategies for new mechanisms of action of antidepressant drugs. Indeed, since the first clinical evidence, in the 60s, that iproniazide and imipramine had mood elevating properties, research has focussed on understanding the mechanism of antidepressant drug action. These early observations, together with the notion that reserpine, a monoamine depletor, induces some of the cardinal signs of depression, provided the foundations for the biogenic amine theory of depression. Since that time, research has produced many *me-too* antidepressants. However, only a portion of the depressed patients is responsive to current antidepressants. Nevertheless, animal models are considered validated only when “classical” antidepressants are active. This tautology is likely to have hampered the progress in the search of new antidepressants. Research in humans also shows several limitations. Although psychiatrists agree on the fact that the population of depressed patients is heterogeneous, only a few attempts have been made to identify subgroups of depressives differentially responding to antidepressants. Thus, current clinical trials have set the primary end-point for significant therapeutic efficacy to a mean 50% reduction in the Hamilton Depression Score, irrespective of a differential impact on specific items. Some responsibility for the failure to find antidepressants with novel mechanism of action also derives from the tendency of the pharmaceutical industry to favour the development of antidepressant drugs capable of treating the whole depressed population, rather than specific subpopulations of depressives. These historical aspects need to be critically evaluated in order to develop new strategies for developing a new generation of antidepressants.