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Review

Antidepressant treatment and rodent aggressive behaviour

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Abstract

This review examines two 'ethologically relevant' rodent models, the resident–intruder and social hierarchy paradigms, that are sensitive to chronic antidepressant treatment (including repeated electroconvulsive shock). These models of rodent social and agonistic behaviour demonstrate that acute and chronic treatment with antidepressant drugs (regardless of their acute pharmacological activity) induce diametrically opposite changes in rodent aggressive behaviour. The common ability of chronic antidepressant treatment to increase rodent aggression (which in turn results in increased hierarchical status in closed social groups) most likely reflects the increased assertiveness and associated externalization of emotions (indicative of increased extrapunitive aggression) expressed during recovery from depressive illness. Finally, findings that relate observed behavioural changes to underlying neurochemical changes are briefly reviewed in terms of adaptive mechanisms in the rodent central nervous system induced by antidepressants, and also with respect to suicide ideation and panicogenic responses observed in some patients at the onset of treatment with selective serotonin reuptake inhibitors for affective disorders.

Keywords: Animal model of depression; Chronic antidepressant treatment; Agonistic behaviour; Social hierarchy; Resident–intruder; Suicide ideation

Contents

1. Introduction

Animal models of depression are used for a variety of purposes: as screening tests to discover and develop novel antidepressant drug therapies; as simulations for investigating aspects of the neurobiology of depressive illness; and as experimental models within which the neuropharmacological mechanisms associated with antidepressant treatments, including the tricyclic antidepressant, selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), and monoamine

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oxidase (MAO) inhibitor drugs and electroconvulsive shock, may be investigated (Henn and McKinney, 1987; Jesberger and Richardson, 1986; McKinney, 1984; Willner, 1984, 1990; Willner and Mitchell, 2002). Whether any single animal model can fulfill all these diverse needs is questionable. The pessimistic view is that currently available animal models are only models of antidepressant activity (including electroconvulsive shock). If this is the case, they may prove adequate as both screening tests and as models to investigate neuropharmacological mechanisms associated with treatment, but their validity as simulations of the psychiatric condition is highly questionable.

The essential requirement for any antidepressant screening test is that it accurately predicts antidepressant activity. Ideally, it should also be cheap, robust, reliable and easy to use (Danysz et al., 1991; Willner, 1991) and should therefore be as simple as possible. Consequently, the majority of animal models used routinely as antidepressant screening tests rely on an acute response to drug treatment. The almost universal use by the pharmaceutical industry since the beginning of the 1970s of drug screening tests sensitive to acute or sub-acute drug treatment has resulted in the discovery of an array of antidepressant drugs all with pharmacological and therapeutic profiles qualitatively similar to that of the archetypal tricyclic antidepressant, imipramine, or MAO inhibitor, isoniazid. The success and consequent continued use of screening tests that rely on acute treatment has undoubtedly restricted the development of animal models with improved face and construct validity with respect to depressive illness, and has also largely been responsible for delaying the development of animal models in which antidepressants are active only following chronic administration. Such animal models are of no value in the drive to identify antidepressant drugs with a more rapid onset and have limited or minimal validity as simulations of depression (Willner, 1984; Willner and Mitchell, 2002). Consequently, the use of acute drug screening models has simply resulted in the identification of further 'me-too' compounds (novel compounds whose acute pharmacological profile is similar to those already available to the clinician), has provided no information on onset of clinical efficacy, has been of very limited use in furthering our knowledge of the mechanisms associated with the psychopathology of depressive illness or adaptive changes associated with the recovery process from depression, and has demonstrably failed to identify novel mechanisms and targets for future drug discovery.

However, the simplistic view that screening tests for antidepressant activity should necessarily rely on an acute response has changed during the last decade. The clinical requirement is now to identify rapid onset antidepressant treatments. Of necessity this approach involves the assessment of drug action associated with chronic/continuous drug treatment regimes and measuring an acute response is of little value, except to gain information regarding drug potency and thereby identify dose levels that may be used in subsequent chronic treatment studies. Appropriate screening tests to be used early during drug development should therefore have the ability to identify the time course of drug action associated with repeated treatment schedules.

The belief that clinical efficacy is dependent on chronic treatment has led to a considerable literature describing the effects of chronic antidepressant administration in normal animals, and numerous changes in pre- and/or post-synaptic receptor function have been reported, in a variety of systems. These studies are an essential first step towards establishing mechanisms of antidepressant action. However, the inability to determine which of the many effects of antidepressants are responsible for their therapeutic actions constitutes a fundamental limitation of this approach. The development of animal models that mimic, chronically, some aspects of the human disease state and which can be challenged with established or putative 'therapies', provides a powerful methodology for investigating these problems.

In contrast to the changing criteria for screening tests for antidepressant drugs, a simulation of depression aims to mimic aspects of the clinical situation. If a model is to be used to investigate antidepressant actions, a measurable, progressive, onset that is comparable to the clinical time course, is highly desirable. The importance of this feature is that only when a model allows detection of a gradual onset of action is it possible to detect a more rapid onset. The model should also respond differently (either in the direction of response or in response magnitude) to single and repeated (chronic/continuous) treatment regimes. One advantage of animal models which are able to identify novel therapies with a rapid, progressive, onset of action is that such animal models provide time-dependent behavioural markers of successful antidepressant treatment. These behavioural markers may then be used to identify concomitant changes in neurochemistry and neurotransmitter receptor-mediated function that may underpin the observed antidepressant-induced change in behaviour and so increase our understanding of the neurochemical mechanisms responsible for antidepressant action. The three models for which the clearest evidence for gradual onset of action exists are Chronic Mild Stress and two models based on the ethological analysis of rodent non-social, social and agonistic behaviour (the resident–intruder and social hierarchy tests) (see Willner and Mitchell, 2002). It is the latter two models that are the focus of this review.

2. Rodent non-social, social and agonistic behaviour

The ethological studies of Dixon and co-workers (Dixon et al., 1989) have shown that increased flight and impaired sociability are significant features of the non-verbal behaviour of patients with depressive illness. Clinical studies also indicate that such abnormal behavioural responses/reactions of patients with depressive illness to environmental and social stimulation are progressively modified during remission from the illness (Eisen, 1989; Khan et al., 1989; Oswald et al., 1972). Thus recovery from a depressive episode is associated with progressively reduced self-criticism and feelings of guilt (Priest et al., 1980) that lead to increased physical and/or verbal interaction with the environmental and social events