The Use of an Animal Model to Study Post-Stroke Depression

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Introduction

The development of an animal model of a medical disorder found in humans provides many research advantages over a purely clinical investigation. The specificity of anatomical, biochemical, or physiological changes can be assessed while controlling for numerous other variables which may or may not be associated with the medical condition. There are numerous examples in literature of the value of investigating animal models. Thus it is not surprising that clinically oriented investigators are always in search of animal models of important human disorders.

When the search for animal models turns to psychiatric conditions such as depression, the problem is more difficult because the etiology of most depressive disorders is not known. Thus, a human condition diagnosed by clinical interview cannot be directly validated in the animal by production of the underlying etiology or by clinical examination. Most animal models are validated only by behavioral observation or response to treatment (the specificity of treatment for the etiology of depression is largely uncertain). These validation techniques leave both clinician and researcher dissatisfied with the relevance of the findings from the animal model to the human condition.

Stroke is a focal neurological deficit occurring over seconds to hours produced by the diminution of blood circulation to a specific area of brain. Stroke can produce any of numerous motor, sensory or behavioral deficits, depending on the particular area of brain involved. For many years, clinicians have recognized that depressive disorders frequently accompany stroke (Bleuler, 1951; Kraeplin, 1921). Since stroke can be experimentally produced in animals, it seems that this would be a possible avenue for studying depressive disorders in animals.

The problem, however, has been the uncertainty of the nature of the relationship between stroke and depression. Many clinicians have assumed that the depressive disorder represents an understandable psychological response to the physical or cognitive impairment. Fisher (1961) stated that the brain
was "the most cherished organ in the body" and that injury to this organ would understandably lead to depression. Systematic studies, however, have tended to refute the assumption that depression could be entirely attributed to the physical or cognitive impairment. Folstein et al. (1977) found that 25 stroke patients were significantly more depressed than 15 orthopedic patients even though the two groups had equal degrees of physical impairment. Epidemiological studies by Kay (1962) found a frequent association between cerebrovascular disease and first episodes of severe endogenous depression in the elderly. Post (1962) found cerebral ischemic lesions in a high proportion of geriatric patients who had been admitted to hospital for treatment of endogenous depression. Recently, Finkelstein et al. (1982) found that depression and failure to suppress serum cortisol following dexamethasone administration was significantly more common in stroke patients when compared with a group of control patients with other chronic medical illnesses; and Sinyor et al. (1986) reported that the severity of depression was not significantly correlated with the severity of physical or cognitive impairment.

Thus, systematic studies have suggested that depression may be a specific consequence of focal cerebral damage just as hemiparesis or visual field defect are the specific consequence of injury to localized brain regions. Because stroke can be experimentally produced in animals, this disorder might lend itself to the production of an animal model of a depressive disorder. Before the effectiveness or usefulness of an animal model can be evaluated, however, it is important to detail the course, symptoms, response to treatment, and associated variables in the clinical condition of post-stroke depression.

Clinical Syndromes

In systematic studies of stroke patients conducted by the author and colleagues, three types of mood disorders were recognized. The first mood disorder is a severe depression that meets the Diagnostic and Statistical Manual III (DSM-III) (American Psychiatric Association, 1980) symptom criteria for major depression. The percentage of patients showing various symptoms of major depression from a consecutive series of 41 patients meeting the diagnostic criteria are shown in Table 1. These disorders are strongly associated with left frontal brain injury. The second mood disorder is a depressive syndrome which meets the DSM-III symptom criteria for dysthymic disorder (termed here minor depression). The percent of patients with minor depression showing various depressive symptoms found in a consecutive series of 41 patients is shown in Table 1. Minor depressions are frequently associated with posterior hemisphere (parietal-occipital lobe) lesions of either hemisphere. The third mood disorder associated with stroke is an indifferent, apathetic mental state associated with inappropriate cheerfulness. This