Notes and Comment

Investigating locomotion abnormalities in animal models of extrapyramidal disorders: A commentary

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Diseases of the extrapyramidal system usually result in disorders of movement, and the location of the pathology within this system is critical in the expression of the type of movement disorder. For example, Huntington's disease, which is characterized by degeneration of basal ganglia neurons, is expressed as abnormal involuntary movements (Sanberg & Coyle, in press), whereas, Parkinson's disease, in which there is a loss of the dopamine afferent system to the striatum, results in rigidity and bradykinesia (Barbeau, 1981). Furthermore, Tourette's syndrome, where a hypersensitivity of striatal dopamine receptors has been postulated (Shapiro, Shapiro, & Wayne, 1973; Singer, Butler, Tune, Seifert, & Coyle, 1982), is characterized by chronic fluctuating motor tics and involuntary verbalizations (Singer, 1982). Thus, alterations in the functions of the basal ganglia are evident in many movement disorders. Unfortunately, the role of this important group of telencephalic nuclei in behavior is little understood. Our research interests have been in trying to understand this role for both the developing and mature striatum (Johnson & Becker, 1973; Polgar, Sanberg, & Kirkby, 1981; Sanberg, Pisa, & Fibiger, 1979). The research discussed here is concerned primarily with analyzing in detail the pattern of abnormal locomotion found in neonatal and adult rats with various types of striatal

lesions. This will add to our comprehension of the role of the striatum in movement and related disorders. Furthermore, this may lead to the development of reliable animal models for human extrapyramidal disorders.

Most patients with extrapyramidal movement disorders show greater abnormal movements during their awake period and when aroused (Shapiro, Shapiro, Brown, & Sweet, 1978; Shoulson & Chase, 1975). Thus, when examining the motor behavior of animal models as an analogue to human movement, it is important to take into account diurnal variations, especially nocturnal activity, in the rat model, since it is at this time that abnormal motor behavior would be most apparent. Almost all previous studies in the rat have limited the behavioral testing to daytime periods. In nocturnal studies that have been performed, however, many types of brain lesions (e.g., cortical, hippocampal, diencephalic, etc.) have been demonstrated to cause hyperactivity similar to that seen in striatal lesioned animals (Thompson, 1978), making it impossible to ascribe specific behavioral deficits to known brain pathology. This is in part because the dependent measures that have been utilized by most investigators as an index of activity (e.g., the number of photocells crossed by an animal) are not sensitive enough to detect species-dependent locomotion abnormalities that are manifested solely by striatal dysfunction. It is likely that the anatomical differences, both neurological (e.g., rats lack a cortical-subthalamic nucleus connection) and morphological (e.g., rats are quadrupeds), between rats and primates limit the ability of rodents to show dyskinetic movements topographically analogous to those of human patients with extrapyramidal disorders. Therefore, it becomes essential to define exactly what species-specific behaviors in the rat are analogous to those in man.

By looking at the animals in a nonnaturalistic setting (e.g., running wheels), previous investigators have not optimized the testing conditions for this. They also failed to obtain an architectural picture of the locomotor abnormalities exhibited by brain-lesion rats. In addition, the paradigms have been contrived, and testing situations, in which only one "activity" variable was measured, have been limited. It is not surprising, therefore, that, with only one such measure, many types of brain manipulations would produce the same result (i.e., increased nocturnal activity). Activity, per se, involves many aspects of movement, such as forward locomotion, velocity, rearings, stereotyped movements, rotational behavior, etc., and an increase in any one of these would produce increased photocell counts,

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and by definition, increased activity. Furthermore, such a limited dependent measure would not allow us to define exactly what the locomotion abnormalities following experimental brain manipulations were.

Using recently developed computerized Digiscan animal activity monitors (Omnitech, Inc.), which simultaneously measure over 20 aspects of locomotion, including many indices of horizontal, vertical, stereotypical, and rotational behavior, recent studies have found locomotor abnormalities that appear to be specific to various types of experimental manipulations (e.g., Sandberg, Sanberg, & Coyle, in press). Perhaps one of the most interesting examples involves the use of the mitotic inhibitor, methylazoxymethanol (MAM). MAM is a potent alkylating agent that ablates actively dividing neuroblasts while sparing cells that have already divided. Thus, the injection of MAM into rats on Day 15 of pregnancy (a time when the striatum and cortex are developing) produces a severe and lasting hypoplasia of these areas in the offspring with a resulting hyperinnervation of ascending neurotransmitter systems to the forebrain (Beaulieu & Coyle, 1981; Johnston & Coyle, 1980). There is evidence of a "genuine hypoplasia, or dwarfism, of the corpus striatum as a consequence of failure of neuronal maturation of the interneuronal neuropil [in Tourette's syndrome] so that the striatum remains arrested at a stage of development normally found in a young child" (Richardson, 1982). Moran, Sanberg, and Coyle (1983) found that the MAM animals have a delayed maturation of inhibitory cortical processes on stimulation-induced behaviors. When we examined these rats for spontaneous locomotion in Digiscan monitors, there were no differences between MAM-treated and age-matched controls during the daytime. However, during the nocturnal period, the MAM-treated rats as compared with controls, demonstrated a pronounced hyperkinesia, as early as Day 10 of age (see Figure 1). Although Day 10 animals showed hyperactivity only on distance traveled, during subsequent development the hyperactivity became apparent on more aspects of locomotion. While the adult MAM-lesion rats traveled farther than control animals, there were no increases in the number of movement bouts or time spent moving. What these animals did show, however, was a greater speed of movement during each bout of activity (see Figure 2). It was of interest that rearing behavior, which emerges on or about Day 15 in the rat (Sanberg, Moran, Kubos, & Coyle, in press), also markedly increased in MAM animals, as did their excursions around the perimeter of the test cage (Sanberg, Moran, Kubos, Antuono, & Coyle, 1983). On the other hand, MAM animals showed no differences from controls in stereotyped behaviors (Sanberg, Moran, Kubos, Antuono, & Coyle, 1983). Thus, the MAM hyperkinesia was characterized by the animals' running around the perimeter of the test cage more often and faster than controls, in addition

Figure 1. The effect of MAM (20 mg/kg/0.5 ml saline) or saline in pregnant Sprague-Dawley rats (Day 15 of gestation) on the activity of their offspring at Day 10 of age (see Johnston & Coyle, 1980, for details). Neonatal rats were tested individually for spontaneous motor behavior in Digiscan animal activity monitors (Omnitech, Inc.) during their nocturnal cycle (8:00 p.m.-8:00 a.m.). Food and water were available during the testing session (see Sandberg, Sanberg, & Coyle, in press, for details). The mean total distance traveled by the pups ($n=6$ males/6 females/group) is depicted for each 2-h period. Analysis of variance revealed significant differences between MAM- and saline-treated animals ($p < .05$).

to rearing more. At present, the effects of various dopamine modulating agents on the abnormal motor behavior exhibited by MAM rats are being studied in order to find out whether there are any alterations in the functional integrity of the neurotransmitter system(s) that could account for this dramatic and persistent hyperkinesia in rats with telencephalic hypoplasia induced by MAM.

This type of naturalistic and multifactorial analysis is critical if we are to characterize the total locomotion architecture of experimentally treated animals, in order to clarify the locomotor analogies between animal models of extrapyramidal disorders and human conditions. Furthermore, because drugs would be tested on many aspects of abnormal movement in the rat, instead of on one gross "activity" measure as previously done, such analysis would produce a more analogous pharmacological screening method for animals. However, before we can make full use of this type of analysis with animal models, studies using normal animals to correlate and standardize this new method of analysis with previously much used methods of behavioral investigation, such as catalepsy, open-field, and stereotypy paradigms, need to be completed. In studies done so far, we have found excellent correlations between the several standard behavioral measures and the animal activity monitor variables (Sanberg, Moran, Kubos, & Coyle, 1983; Sanberg et al., in press).

With the use of this multifactorial approach to animal locomotion, it should be possible to test experi-

Figure 2. The effect of MAM (20 mg/kg/0.5 ml saline) or saline in pregnant Sprague-Dawley rats (Day 15 of gestation) on the activity of their offspring at 3 months of age (see Johnston & Coyle, 1980, for details). The rats were tested individually for spontaneous motor behavior in Digiscan animal activity monitors (Omnitech, Inc.) during the nocturnal cycle (8:00 p.m.-8:00 a.m.). Food and water were available during the testing session (see Sandberg, Sanberg, & Coyle, in press, for details). Mean horizontal activity (number of infrared beams broken by the animal in the horizontal plane), total distance traveled, and the average speed of the rats ($n=6$ males/6 females/group) are depicted for each 90-min period. Analysis of variance revealed significant differences between MAM and saline treated animals ($p < .05$).

mental therapeutic agents on species-dependent abnormal behaviors in rodent models of extrapyramidal disorders that are mechanistically more analogous with the human condition. Additionally, these detailed locomotion analyses should help clarify the extent of abnormal movements exhibited by animal models, and also contribute greatly to our under-

standing of the role of the striatum in spontaneous and drug-induced movement.

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