BMY 21502 and piracetam facilitate performance of two-choice win-stay water-escape in normal rats*

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Summary. Sprague-Dawley rats given either 5 or 10 mg/kg of a new compound, BMY 21502, 150 mg/kg of piracetam or a dose of methylcellulose vehicle (p.o.) daily for 38 days beginning two days before training were compared on performance of a win-stay water-escape task in a circular water maze requiring the use of working memory. The task involved giving the rats pairs of trials in which the location of a submerged escape platform remained the same within a pair of trials but changed semirandomly across pairs. Rats receiving either 5 mg/kg BMY 21502 or piracetam made more correct choices than did rats receiving only the vehicle (p < 0.05 in each case). The facilitated performance was associated with making fewer perseverative responses that resulted in errors.

Keywords: Cognitive enhancer, working memory, water maze, win-stay, perseveration, nootropic, memory, rodents.

Introduction

During the past 20 years there has been an ever increasing effort to develop drugs to enhance cognitive function, especially in subjects experiencing dysfunction (Wenk and Olton, 1989). Piracetam, a nootropic that is a substituted pyrrolidinone, has been studied extensively for nearly two decades (Gamzu et al., 1989). While its mechanism of action remains uncertain (Tacconi and Wurtman, 1986), the drug has enhanced habituation of exploratory behaviour (Platel et al., 1984), performance of active (Valzelli et al., 1980) and passive (Bartus et al., 1981; Yamada et al., 1985) avoidance tasks, and acquisition of an operant discrimination task (Krejci and Dlabac, 1984) whether used alone or in combination with choline. Piracetam has also protected rats from the amnesic effects of hypoxia (Giurega et al., 1971; Sara and Lefevre, 1972) and Hemicholinium-3 (Franklin et al., 1986), but not scopolamine (Petkov and Vug-
lenova, 1985), and diminished the effects of early sensory deprivation (Mysli-
vecek and Hassmannova, 1973). However, it failed to enhance performance on
shock avoidance tasks in mice (Vincent et al., 1984), younger and older rats
(Means et al., 1980a), and medial thalamically-lesioned rats (Abbot and Means,
1979). Further, piracetam did not facilitate food-reinforced discrimination in
either normal or thalamically-lesioned rats (Means et al., 1980b).

A few studies examined the effects of piracetam on tasks that require animals
to use working memory. Piracetam facilitated performance on an indirect de-
layed response task by some monkeys (Bartus and Dean, 1981). In rats, pir-
acetam increased exploration of a novel object over a “familiar object” (En-
naceur et al., 1989) and, when piracetam was combined with pentoxifylline and
dietary choline chloride, it improved acquisition in a radial arm maze (Olton
and Wenk, 1984). Piracetam alone impaired performance in a radial arm maze
by rats (Beatty et al., 1985).

Recently, BMY 21502, a novel substituted pyrrolidinone, has been identified
as a potential cognitive enhancer (Mattson et al., 1988) (see Fig. 1). BMY 21502
protected rodents from ECS-induced amnesia in a step-down passive avoidance
task. It also facilitated three of four monkeys on acquisition of shape discrim-
ination, but not on performance of a shape delayed matching-to-sample task
(Fitten et al., 1990).

The present study was designed to examine the effects of chronic admin-
istration of BMY 21502 or piracetam on a water-escape task requiring the use
of working memory.

**Materials and methods**

Subjects were 32 male Sprague-Dawley rats that were 141 days old at the beginning of the experiment. They were bred in the East Carolina University Colony and were experimentally naive. Subjects were housed singly in stainless steel wire mesh cages in a room maintained at 22 ± 1 °C with a 16/8 hr light/dark cycle (lights on at 0700 hrs). All subjects had continuous access to food and water.

The apparatus, described elsewhere (Comer and Means, 1989), consisted of a circular metal water tank, 140 cm in diameter by 60 cm high, filled with water to a depth of 25 cm. The tank was divided into radial thirds by clear nylon twine strung 15 cm above the rim. The center of the arc formed by the outer wall of one section served as the starting position for all trials.

Non-toxic white paint was added to the water to camouflage a white, plastic escape platform, 20 cm in diameter, which was placed at the center of the line bisecting either the