Effect of lithium carbonate and α-methyl-*p*-tyrosine on audiogenic seizure intensity

Jobe, Picchioni & Chin (1973) presented evidence that endogenous noradrenaline functions as a modulator of audiogenic seizures in rats and found it to be more active than dopamine on this parameter. The effects of α-methyl *p*-tyrosine (α-MT) and, lithium carbonate on audiogenic seizures have been examined. Both of these drugs produce significant effects on brain noradrenaline. α-MT is a potent inhibitor of tyrosine hydroxylase (Spector, Sjoerdsma & Udenfriend, 1965), and lithium carbonate increases both the uptake and the intraneuronal inactivation of noradrenaline (Colburn, Goodwin & others 1967; Schildkraut, Schanberg & others, 1967; Kuriyama & Speken, 1970).

Female rats (150–250 g) of the University of Arizona colony susceptible to audiogenic seizures were given α-MT (80 mg kg^{-1}, i.p., every 4 h for 3 doses) as a suspension in normal saline; lithium carbonate (20–40 mg kg^{-1} twice daily) was dissolved in deionized water and administered orally. The severity of the seizures was quantitated by use of a scoring system, composed of audiogenic response scores from 0 to 9, arranged so that each higher score represented a more intense seizure (Jobe & others, 1973).

The results show that simultaneous administration of lithium carbonate and α-MT markedly enhanced the intensity of seizures, whereas each drug administered singly had no effect (Table 1). These data can be interpreted in light of the report by Corrodi, Fuxe & others (1967) that the combination of lithium plus α-MT produced a severe depletion of brain noradrenaline stores in rats, whereas α-MT alone produced only a moderate decrease, and lithium produced no effect at all. In comparison, α-MT depleted brain dopamine to as great an extent as did lithium plus α-MT. Lithium alone produced only a slight decrease in dopamine levels.

These observations lend further support to the concept (Jobe & others, 1973) that seizure enhancement correlates better with severely low noradrenaline levels than with low dopamine levels. A moderate decrease in brain noradrenaline may occur without an accompanying change in seizure intensity. These findings provide confirming

Table 1. *Effect of lithium carbonate and α-MT on the intensity of audiogenic seizure.*

Treatments*	Audiogenic response 167 h after beginning of experiment (Score ± s.e.)
Saline control	2·50 (10)** ± 0·35
Lithium	2·57 (7) ± 0·41
α-MT	2·13 (8) ± 0·13
Lithium + α-MT	5·88 (8) ± 0·99 $P<0·005$

* Treatment schedules: Lithium carbonate was administered orally every 12 h for 13·5 days. The dose was 40 mg kg^{-1} day^{-1} for the first 8 days and 80 mg kg^{-1} day^{-1} thereafter. α-MT (80 mg kg^{-1}) was administered every 4 h for doses beginning exactly 6·5 days (156 h) after the first dose of lithium carbonate. Animals given only lithium carbonate or α-MT were administered saline by appropriate routes so that they were given the same number of injections as animals receiving lithium plus α-MT. Controls were similarly treated with saline only.

** Number of animals.

evidence of the importance of noradrenaline as a modulator of audiogenic seizures.

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Ulcerogenic potential of indomethacin in arthritic and non-arthritic rats

Gastrointestinal disturbance is a well-known effect following excessive doses of steroidal and non-steroidal anti-inflammatory agents (Somogyi, Kovacs & Selye, 1969). Single or multiple doses of indomethacin induce intestinal ulcers in a dose-related manner (Anderson, 1965). Food restriction or bile duct ligation inhibited or significantly reduced the incidence of intestinal ulcers induced with indomethacin or the fenamates (Wax, Clinger & others, 1970; Brodie, Cook & others, 1970). Similarly, catatoxic steroids have also been reported to inhibit indomethacin-induced intestinal ulcers (Selye, 1969).

For several months we have been concerned with studies comparing new non-steroidal anti-inflammatory agents with known standards in several anti-inflammatory and ulcerogenic assays. Since these agents are primarily used only after inflammatory symptomology is evident, it is reasonable to evaluate the ulcerogenic potential of indomethacin at various time-intervals during the development of an adjuvant-induced polyarthritis.

150 male rats (Charles River, Lewis Strain), 170 $\pm$ 10 g were arranged in groups of 5, as summarized in Table 1. Sixty-five rats received an injection of *Mycobacterium butyricum*[1] (250 μg in 0·1 ml sesame oil) in the plantar area of the left hind paw on day 1. The remaining rats served as non-arthritic animals. The arthritic and non-arthritic rats were further arranged into subgroups and indomethacin was administered subcutaneously, (once only) at doses ranging 3·75–30 mg kg^{-1} on day 1, 14 or 28. The animals were killed 24 h later and the small intestine was removed from duodenum to caecum and the inner surface was graded for ulcer incidence and severity (graded 0 to + 3).

Indomethacin at all doses significantly inhibited the *Mycobacterium butyricum*-induced rat paw oedema at 24 h. In the arthritic and non-arthritic rats, the administration of indomethacin at 7·5, 15 and 30 mg kg^{-1}, s.c. on day 1 or 14 induced intestinal ulcers in a dose-related manner. Comparable intestinal ulcers were obtained in both the arthritic and non-arthritic rats at these time intervals. However, a higher incidence

[1] Difco Laboratories, Detroit, Michigan.