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In Vivo Spectrophotometric Determination of Striatal Acetylcholinesterase Activity: The Modulation Induced by the Antidepressant Amitriptyline

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Abstract: A new technology called in vivo spectrophotometry was applied to the quantitative determination of the variations in local acetylcholinesterase (AChE) activities. Repeated measurements of the enzyme activities in the same live animal allowed the study of the in vivo inhibition of AChE by amitriptyline. Interactions between AChE and this tricyclic antidepressant were investigated at the striatal level in anesthetized rats. In this anesthetized model, AChE assays were shown to be stable for ~8 h. The dose-effect relationship was explored in the 2.5- to 50-mg/kg amitriptyline range. A reversible inhibition was observed after acute amitriptyline administration. The maximum of inhibition appeared between 90 and 210 min after the intoxication and reached up to 22% for the 50-mg/kg dose. The threshold dose was established as 8 mg/kg. Evidence for an indirect interaction between tricyclic antidepressant and AChE was demonstrated when the total integrity of the biological system was preserved.
Key Words: Acetylcholinesterase—In vivo spectrophotometry—Striatum—Tricyclic antidepressant—Amitriptyline—Rat. **Chappey O. et al.** In vivo spectrophotometric determination of striatal acetylcholinesterase activity: The modulation induced by the antidepressant amitriptyline. *J. Neurochem.* **54,** 333–338 (1990).

The effects of drugs on brain enzyme activities in physiological situations have not been widely studied in the past, owing to the lack of well-adapted in vivo technologies. Recently, an in vivo spectrophotometric method has been developed that allows direct and localized determination of acetylcholinesterase (AChE) activity in brain tissue of live animals (Testylier and Gourmelon, 1987). In this technique an optical probe consisting of a multibarrel micropipette for reagent injections and optical fibers for light absorption measurements is implanted in a brain structure of an anesthetized animal. This system allows the study in situ and in real time of a colorimetric reaction such as the Ellman reaction used for AChE detection. The reproducibility of the assay has been demonstrated by repeated assays and its specificity has been established through the use of a highly specific organophosphorous inhibitor, methylphosphonothionate (Bajgar and Patocka, 1977).

It seemed interesting to study the modulation of AChE activity in a complex situation by means of this method. Many central-acting compounds were found to exert multiple biochemical interactions rather than specific biochemical activity. Some of them can indirectly interact with the enzyme, through membrane modifications or receptor regulations, for example. In these cases the anatomical and physiological integrity of the biological system is essential for analysis of the phenomenon and consequently in vitro analyses are often doubtful.

Tricyclic antidepressants (TCAs) could belong to this class of compounds. They are known to interfere with the biogenic amine system, mainly with norepinephrine and serotonin (Hollister, 1986), but then also seem to act on the cholinergic system. Indeed, even at therapeutic doses, TCAs induce many adverse anticholinergic side-effects (Blackwell, 1981); cardiac disorders (Glassman, 1984) and peripheral autonomic syn-

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Abbreviations used: AChE, acetylcholinesterase; AUC, area under the curve; TCA, tricyclic antidepressant.