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Effects of Amitriptyline on Serum Glutamate and Free Tryptophan in Rats

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Summary. In rats, chronic amitriptyline (14 days, 10 mg/kg, IP) administration resulted in a significant increase in the serum glutamate concentration and concomitant increase in the serum free tryptophan. In contrast, amitriptyline had no effect on the total serum tryptophan or CSF glutamate level. The data confirmed that antidepressant drugs may induce an increase of the serum glutamate concentration in depressive patients.

Key words: Serum glutamate – Free tryptophan – Amitriptyline – Depression

Zusammenfassung. Die chronische Gabe von Amitriptylin (2 Wochen, 10 mg/kg, i.p.) führte zu einer signifikanten Zunahme von Glutamat und freiem Tryptophan im Serum von Ratten. Dagegen hatte Amitriptylin eine Wirkung weder auf das Gesamttryptophan im Serum noch auf den Glutamatgehalt des Liquors. Diese Ergebnisse bestätigen die Hypothese, daß Antidepressiva für die Zunahme des Serumglutamats bei Depressiven verantwortlich sind.

Schlüsselwörter: Serum-Glutamat – freies Tryptophan – Amitriptylin – Depression

Introduction

Although tricyclic antidepressants are widely used in the treatment of depression, their mechanism of action remains unclear. Most of these drugs are known for their ability to inhibit noradrenaline and serotonin uptake into presynaptic monoaminergic nerve terminals (Glowinski and Axelrod 1964; Carlsson et al. 1969; Iversen 1974). Inhibition of presynaptic uptake increases the availability of noradrenaline and serotonin at postsynaptic receptor sites and thus prolongs and potentiates transmitter function. This has been supposed to be the important mechanism of action of these drugs. However, this inhibition of uptake by the

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tricyclic antidepressants occurs within minutes (Ross and Renyi 1975) whereas the therapeutic effect of these drugs requires a minimum of 8 days (Oswald et al. 1972). Furthermore, recent neurochemical studies suggest that postsynaptic blockade changes in receptor sensitivity and receptor number after tricyclic antidepressant therapy point to the need to reevaluate the site and the mechanism of action of these drugs (Charnley et al. 1981; Tang et al. 1981). Although tricyclic antidepressants are known for a number of peripheral side effects, so far none of these peripheral effects is believed to have an antidepressant effect. In the preceding paper we reported an increase in serum glutatmate in depressive patients, who had been on antidepressant treatment up to 3 days before sample collection (Kim et al. 1983). Data from these patients make it likely that this increase in glutamate represents a long-lasting effect of the antidepressant treatment.

The purpose of our experiments was to verify this hypothesis after chronic administration of the most used tricyclic antidepressant agent, amitriptyline, in an animal model. In addition, we have measured total and free tryptophan levels in serum.

Methods

In all 25 male CHBB rats weighing approximately 300 g were separated into two groups. One group received amitriptyline at a dose of 10 mg/kg IP for a period of 14 days. The control group received an equal volume of isotonic saline solution for 14 days. The animals had free access to food and water. On the 15th day the rats received no further medication and were anaesthetized with Evipan. To obtain CSF, the atlanto-occipital membrane was exposed and approximately 120 µl of CSF were taken from the cisterna magna using a microsyringe. Blood samples were collected by puncture of the aortic bifurcation. Total and free tryptophan in the serum were determined by the method of Eccleston (1973) with some modifications (Bloxam and Warren 1974). Glutamate was measured by the enzymatic fluorometric method (Graham and Aprison 1966). The significance of the difference between treated and controls was calculated by Mann-Whitney *U*-test.

Results

The Table 1 summarises the results. There is a significant increase in serum glutamate after 14 days of amitriptyline treatment as compared to controls ($P<0.05$, +11%). No significant changes in glutamate occurred in the CSF although a slight tendency towards an increase in glutamate occurred in the CSF. Surprisingly, there was a marked increase of free tryptophan after chronic administration of amitriptyline ($P<0.002$, +63%). No change was observed for total tryptophan values. Moreover, no significant correlation between glutamate and free tryptophan could be found.

Discussion

Long-term administration of amitriptyline led to a rise in serum glutamate. The increase after 2 weeks of treatment with amitriptyline was significant. The

Table 1. Effect of amitriptyline 14 days after IP injection (10 mg/kg) on glutamate, free tryptophan, and total tryptophan levels in rat serum and CSF

	Control ($N=12$)	Amitriptyline ($N=13$)
Glutamate		
Serum	236.4±7.3	273.0±10.3*
CSF	16.6±1.7	17.4± 1.6
Tryptophan in serum		
Free	5.3±0.2	8.9± 1.3**
Total	58.7±1.6	53.3± 1.6

* $P<0.05$
** $P<0.002$

increase in serum glutamate in treated depressive patients, which we reported in a preceding paper (Kim et al. 1983) is clearly more marked than the one reported here, which may be due to species differences or duration of treatment. As the non-significant change in CSF glutamate levels shows, the rise in serum glutamate represents a mainly peripheral effect. Serum glutamate is determined mainly by dietary uptake and transport and metabolism in gut and liver (Pardridge 1979). In addition, hyperthyroidism and increased corticosteroids are known to increase serum glutamate (Munro 1979). Here lie possible mechanisms for amitriptyline to influence the level of glutamate. So far the significance of the rise in serum glutamate can be evaluated only vaguely.

The way which amitriptyline leads to a rise in free tryptophan while total tryptophan remains unchanged, is not evident either. Amitriptyline possibly competes with tryptophan for albumin binding and thereby leads to a rise in free tryptophan.

Another possible explanation could be an increase in free fatty acids by amitriptyline and thereby a removal of tryptophan from its albumin binding. Though the mechanism of tricyclic antidepressants is still unknown, until now only central mechanisms like reuptake inhibition, postsynaptic blockade and changes in receptor sensitivity and number are presumed to be responsible for the antidepressant effect. The increase of free trypotphan in serum with amitriptyline could however represent an additional mode of action by which amitriptyline influences the serotoninergic system. Attempts to clarify the role and the mechanism of the rise in serum glutamate and free tryptophan will require further investigation.

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