Influence of tianeptine and clomipramine on the electrical activity of rat monoaminergic neurons and hippocampus pyramidal cells.

Tianeptine (T) is a new potential antidepressant (AD) active in classical pharmacological tests used for AD screening. Biochemical studies *ex vivo* indicate that T increases 5-HT uptake after acute and chronic administration without modification of NA uptake. This property differentiates T from classical tricyclic AD which are potent inhibitors of 5-HT and/or NA uptake.

Electrophysiological studies were performed in order to compare the influence of T and clomipramine (CIMI) on the firing rate of central locus coeruleus (LC) noradrenergic neurons, dorsal raphe (DR) serotoninergic neurons and hippocampus CA1 pyramidal cells.

The interaction of T and CIMI with the response of CA1 cells to iontophoretically applied 5-HT or GABA was also investigated.

Multibarrel glass micropipettes were implanted stereotaxically in male Wistar rats anaesthetized with chloral hydrate. The central barrel filled with NaCl 2% saturated with fast green was used for recording action potentials. Side barrels were filled with a solution of acetylcystine chloride 0.02m in NaCl 0.2m pH 4, GABA 0.01m in NaCl 0.1m pH 4, 5-HT creatine sulphate 0.02m in NaCl 0.02m pH 4, CIMI HCl 0.1m pH 4 or T 0.1m pH 9 and NaCl 4m for automatic current balance.

In systemic studies T or CIMI were perfused into the jugular vein by means of a perfusion pump (flow 6 ml/h). In iontophoretic studies, 5-HT or GABA were applied by pulses of 60 s at constant current before, during and after the iontophoretic application of T or CIMI.

In systemic studies the dose of drug required to produce a 50% inhibition (ID₅₀) or activation (ED₅₀) of the firing rate was calculated. In iontophoretic studies, the responsiveness of CA1 cells to 5-HT or GABA was evaluated by calculating the mean percent inhibition produced by the ionophoresis of 5-HT or GABA. Statistical analysis was performed using Student’s *t* test for paired samples. The recovery after 5-HT or GABA was measured by calculating the percentage of recovery 10, 20 and 30 s after the iontophoretic application. Statistical comparison of the recovery curves was realized using Zerbe method.

The i.v. perfusion of CIMI decreases the firing rate of DR, LC and CA1 neurons. The i.v. perfusion of T does not modify the firing rate of DR neurons, decreases the firing rate of LC neurons and increases the firing rate of CA1 pyramidal cells. Quantitative values are given in Table I.

The iontophoretic application of CIMI (6-10 nA) on CA1 neurons selectively potentiates the responsiveness of these cells to 5-HT (*P* < 0.01) but not to GABA. The

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<th>Table I. Mean (± SE) effective doses (in mg/kg) of CIMI or T required to produce a 50% inhibition or activation of LC, DR or CA1 pyramidal cells after i.v. perfusion. <em>n</em> = number of animals.</th>
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Iontophoretic application of T (10-14 nA) does not induce a significant modification of the responsiveness of CA1 cells to 5-HT or GABA. The iontophoretic application of CIMI significantly increases the recovery time after 5-HT (P<0.005).

The iontophoretic application of T significantly decreases the recovery time after 5-HT (P<0.001) and GABA (P<0.005).

T and CIMI differ in their influence on the firing rate of monoaminergic neurons and CA1 pyramidal cells.

The inhibitory effect of CIMI on the firing rate of DR and CA1 neurons after i.v. perfusion is probably related to an increased availability of 5-HT in the synaptic cleft due to the uptake inhibition. The similarity between the ID50 values supports this interpretation. Furthermore, iontophoretic studies with CIMI show a selective potentiation of the inhibitory effect of 5-HT on CA1 cells.

The unspecific effect of CIMI on the recovery time after 5-HT or GABA may be related to the inhibitory effect of CIMI itself on the firing rate of CA1 cells after prolonged application.

The effect of CIMI on LC neurons may be related to its weak inhibitory effect on NA uptake.

T has no effect on the firing rate of DR neurons, decreases the firing rate of LC neurons and increases the activity of CA1 cells. The activation of CA1 cells seems in agreement with an increased uptake of 5-HT. However, the only indication of an interaction between T and 5-HT mechanisms in our studies is the decreased recovery time after 5-HT and this effect is not specific as the recovery time after GABA is also decreased.

In conclusion: T appears to have an original electrophysiological profile in comparison with classical AD. Its mechanisms of action remain to be elucidated.

Reference


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