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THE EFFECT OF CYPROHEPTADINE AND AMANTADINE ON NEUROLEPTIC-INDUCED CATALEPSY IN THE RAT

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SUMMARY

Catalepsy is not a unitary phenomenon. With respect to biochemical mechanisms and neurotransmitter sytems, the origin of this behavioural response varies according to different substances which cause catalepsy. For example, the cataleptogenic effect of neuroleptics has been related to the blockage of striatal dopamine receptors. Neurophysiological and biochemical data have shown that a mechanism caused by gama-aminobutyric acid and serotonin have been effective in the proper functioning of the dopaminergic nigrostriatal tract.

We have studied the effects of cyproheptadine, a serotonin antagonist, and of amantadin which is used in the treatment of Parkinson syndrome on the catalepsy induced by trifluoperazine, a phenothiazin compound, and pimozid, a drug used as a neuroleptic. It was observed that when rats were pretreated with cyproheptadine as well as amantadine, the catalepsy induced by the above neuroleptic drugs was attenuated.

The results of our study show that substances which have an effect on the serotonergic and dopaminergic systems also play a role on cases of catalepsy induced by the neuroleptic drugs mentioned above.

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ÖZET

Katalepsi bir tek nedene bağlı olarak ortaya çıkan bir durum değildir. Biyokimyasal ve nörotransmitter sistemler açısından bu davranışın sebebi, katalepsi oluşturan çeşitli maddeler için farklıdır. Örneğin nöroleptiklerin kataleptojenik etkisi striatal dopamin reseptörlerinin blokajına bağlanmıştır. Nörofizyolojik ve biyokimyasal veriler dopaminerjik nigro-striatal sistemin düzenli çalışmasında gama-aminobutirik asid ve serotonin'e bağlı olan bir mekanizmanın etkili olduğunu göstermiştir.

Bir serotonin antagonisti olan siproheptadin'in ve Parkinson sendromunun tedavisinde kullanılan amantadin'in; fenotiazin bileşiği olan trifluperazin ve nöroleptik olarak kullanılan ve etkili bir ilaç olan pimozid'in yaptıkları katalepsiye etkilerini inceledik. Sıçanlara önceden siproheptadin verildiğinde yukarıda belirtilen ilaçların neden olduğu katalepsinin şiddetinin azaldığı görüldü. Diğer yandan sıçanlara önceden amantadin verildiği zaman, aynı nöroleptik ilaçların ortaya çıkardığı katalepsinin de geç ortaya çıktığı gözlendi.

Çalışmamızın sonuçları yukarıda belirtilen nöroleptik ilaçların neden olduğu katalepside, serotonerjik ve dopaminerjik sistemlere etkili olan siproheptadin ve amantadinin de rolü olduğunu göstermektedir.

Key words: Catalepsy, neuroleptic, cyproheptadine, amantadine.

INTRODUCTION

Catalepsy, currently viewed as a symptom common to many pathological states, e.g. catatonic schizophrenia and extrapyramidal disorders, can be elicited experimentally by a variety of compounds. The origin of this behavioral response from the standpoint of biochemical and neurotransmitter systems is apparently different for various agents which induce this state of catalepsy. For example the cataleptogenic effect of neuroleptics has been attributed to blockade of striatal dopamine receptors (1). These drugs produce catalepsy in rats and also increase the dopamine turnover and the accumulation of its metabolites (2, 3). This cataleptogenic effect is not special to neuroleptics only, but it is also produced by non-neuroleptic drugs (4, 5, 6). Morphine and other narcotic analgesics which are non-neuroleptic drugs induce catalepsy in rats (7). Another important factor observed in the catalepsy in rats is the mechanisms which act as regulators between different neurotransmitter systems.

Neurophysiological and biochemical evidences indicate that gama-aminobutyric acid (GABA)-mediated and serotonin (5-HT)-mediated mechanisms are involved in the-regulation of the dopaminergic nigro-striatal tract (8, 9, 10). It has been shown that 5-HT has a marked effect on the ability of GABA-ergic mechanisms to potentiate the cataleptogenic effects of the dopaminergic antagonist α-flupenthixol (11). On the other hand it is proposed that the 5-hydroxytryptaminergic regulation of nigro-striatal dopaminergic activity could be mediated via a *post-synaptic* action of 5-HT which releases dendritic dopamine and in turn leads to a release of GABA (12).

In our study, we examined the effect of cyproheptadine and amantadine pretreatment on the catalepsy induced by trifluoperazine and pimozide.

MATERIAL and METHOD

Male Wistar rats weighing between 200-250 g were used throughout all experiments. Animals were normally housed in groups of six and allowed food and water ad libitum. Catalepsy measurements were performed in a quiet laboratory with the temperature maintained constant at 22 ± 1°C. In each experiment, 12 rats were used per dose. Catalepsy was measured by the horizontal bar test. The rats were placed with their forelegs on a wooden bar 9 cm above the ground. Catalepsy was evaluated every 30 min for 2 hrs following the administration of pimozide and trifluoperazine. Thereafter, the time for which the animal maintained this posture was measured every 60 min. The scoring system used for the estimation of the intensity of catalepsy: Animals maintaining the cataleptic posture from 0 to 15 sec. = 0; 15 sec. to 2 min. = 1; 2 to 4 min. = 2; 4 to 6 min. = 3; more than 6 min. = 4. A time limit of 5 hrs was placed on each experiment.

All drugs were injected intraperitoneally. Control animals received vehicles which were used for dissolving the drugs.

Amantadine HCI (50 mg/kg), trifluoperazine HCI (3 mg/kg) and cyproheptadine HCI (2 mg/kg) were dissolved in distilled water. Pimozide (4 mg/kg) was dissolved in 1.5 % tartaric acid solution.

Trifluoperazine HCI and Pimozide were injected one hour after the administration of cyproheptadine HCI or amantadine HCI.

Amantadine HCI, trifluoperazine HCI, cyproheptadine HCI and pimozide were kindly gifted from Yurtoğlu Farma İlaç Sanayii A.Ş., Dr. F. Frik İlaç Sanayii ve Ticaret Ltd. Şti., Dr. İbrahim Etem Ulagay İlaç Sanayii T.A.Ş. and Doğu İlaç Fabrikası A.Ş., respectively. Tartaric acid was obtained from Merck, Darmstadt.

The results were analysed statistically using Student's t-test.

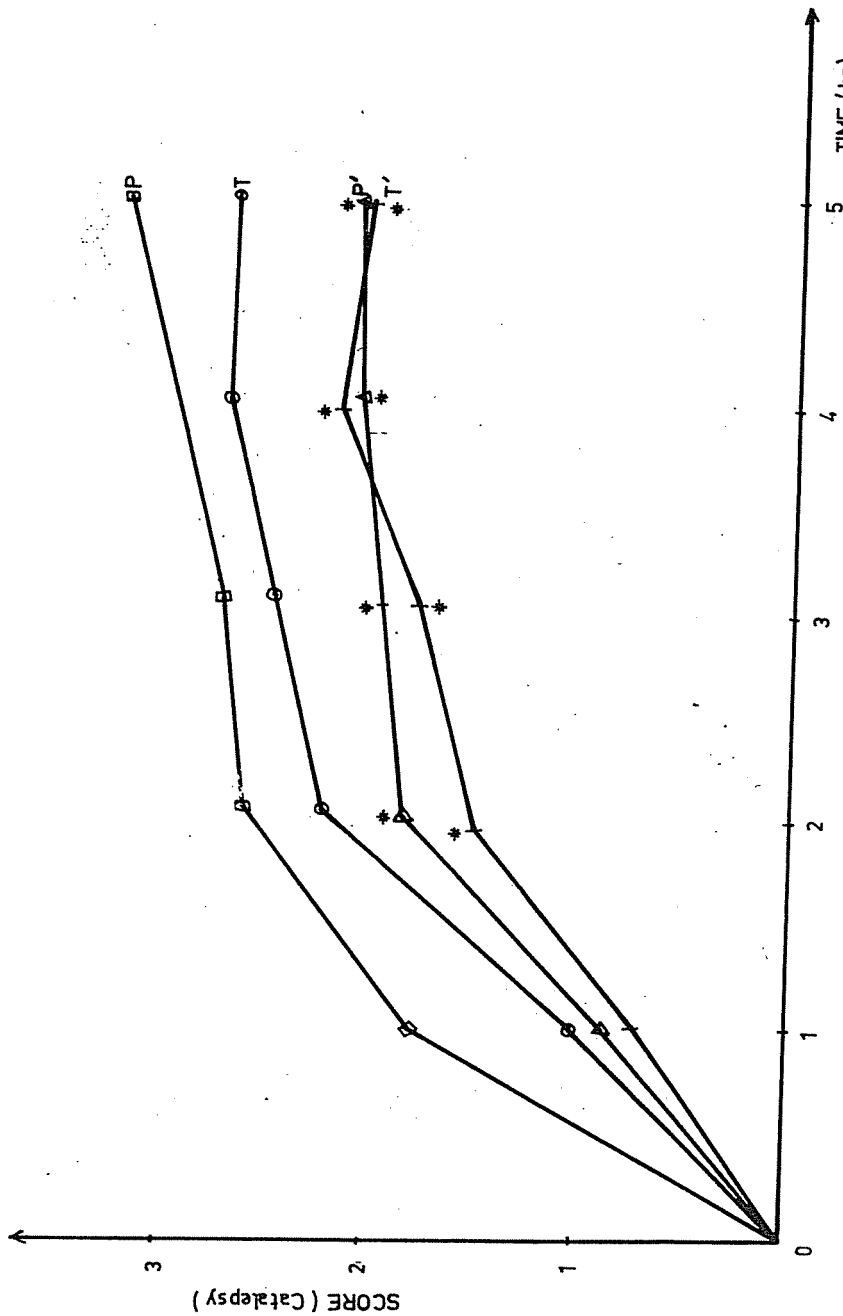

Figure 1: The figure shows the catalepsy scores plotted against time. P pimozide, T trifluoperazine, P' pretreated with cyproheptadine + pimozide, T' pretreated with cyproheptadine + trifluoperazine. Statistical comparisons were made between groups P and P', and T and T'.
* Significant difference ($p < 0.01$) from the relevant test group.

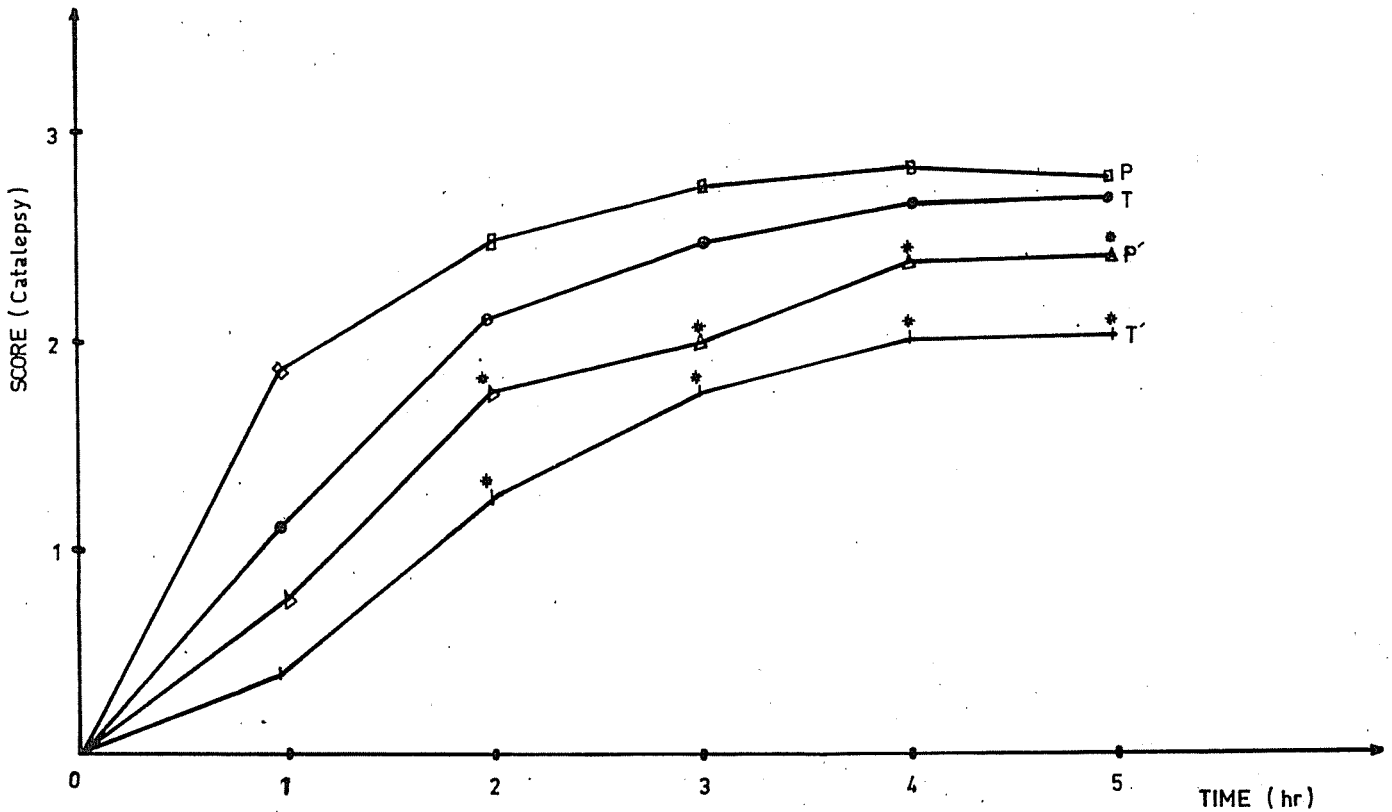

Figure 2: The figure shows the catalepsy scores plotted against time. P pimozide, T trifluoperazine, P' pretreated with amantadine + pimozide, T' pretreated with amantadine + trifluoperazine. Statistical comparisons were made between groups P and P', and T and T'.
* Significant difference ($p < 0.01$) from the relevant test group.

RESULTS and DISCUSSION

Selective D_2 antagonists such as pimozide induce catalepsy in rats, like mixed D_1 / D_2 antagonists such as trifluoperazine HCI. Different neuronal networks containing transmitters may be involved in the catalepsy caused by D_2 and D_1 receptor antagonists.

In this study, it was observed that when the rats were pretreated with cyproheptadine, the catalepsy induced by pimozide and trifluoperazine was attenuated (Figure 1). On the other hand when the rats were pretreated with amantadine, the catalepsy induced by the same neuroleptic drugs was also attenuated (Figure 2).

It has been shown that amantadine, an antiviral agent, D_1 agonist and DA releaser, antagonizes prochlorpemazine induced catalepsy (13). On the other hand cyproheptadine, a $5HT_2$ serotonin antagonist also attenuates catalepsy induced by some phenothiazine compounds (14).

The results of this study show the role of serotonergic and dopaminergic agents in modulation of catalepsy induced by the above mentioned neuroleptic drugs. Also these results suggested an interaction between D_1 and D_2 receptors in producing catalepsy.

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