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Research Report

Adverse effects of antipsychotics on micro-vascular endothelial cells of the human blood–brain barrier

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ABSTRACT

Although the mechanisms of action of antipsychotics (APs) on neuronal function are well understood, very little is known about their effects on cells of the blood–brain barrier (BBB); one function of which is to limit the access of these amphiphilic compounds to the central nervous system. To address this question we have investigated the cytological and functional effects of four APs: chlorpromazine (CLP), haloperidol (HAL), risperidone (RIS) and clozapine (CLZ), at concentrations typical of high therapeutic dosage on a human brain microvascular endothelial cell (HBMEC) model of the BBB. At ~10 μM all four APs impaired the ability of HBMECs to reduce MTT which was followed by decreased Trypan blue exclusion and increased Lactate dehydrogenase release. These effects were associated with oxidative stress which was partly reversed by incubation in 10 mM glutathione. At their EC_{50} concentrations for MTT reduction, all four APs disrupted cellular ultrastructure and morphology. HAL, CPZ and CLZ increased Caspase -3, -8 and -9 activity, chromatin condensation and fragmentation, data indicative of apoptosis. These events were associated with decreased transcytosis of Evans blue and increased transendothelial potential difference and electrical resistance of this BBB model. These findings suggest that at high therapeutic concentrations, CPZ and CLZ are likely to incur cytoxic effects and apoptosis of BBB endothelia with an impairment of barrier functionality. Such events may underlie the aetiology of neuroleptic associated cerebral oedema and neuroleptic malignant syndrome.

1. Introduction

Antipsychotics (APs) are widely prescribed to manage psychoses that occur with schizophrenia and bipolar disorder (Miyamoto et al., 2005). Initially thought to achieve their therapeutic outcome by blockade of central dopaminergic and serotonergic pathways, however, APs are now known to involve a wider range of receptor targets which may,

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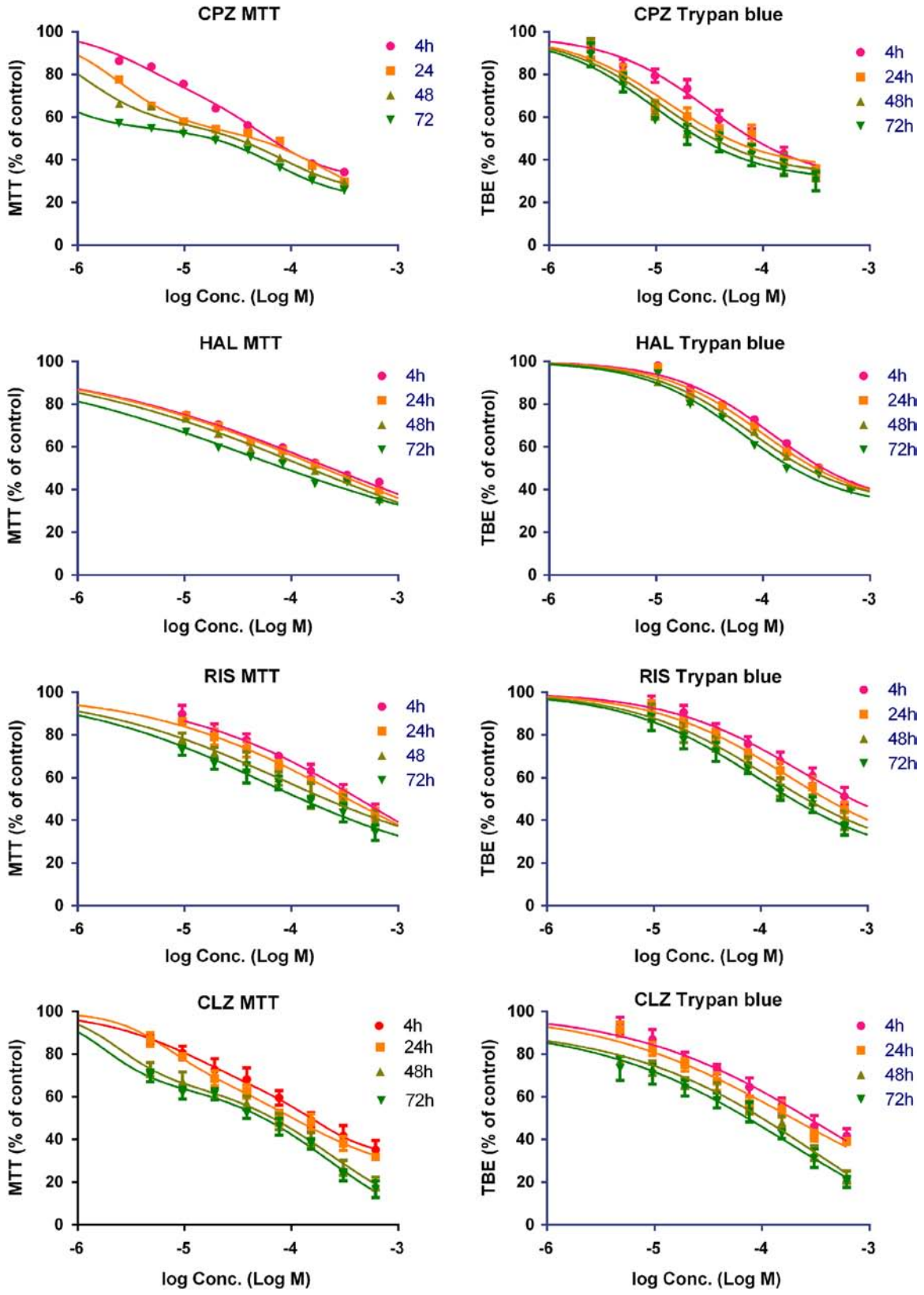

Fig. 1 – Concentration–effect relationships for the effect of chlorpromazine (CPZ), haloperidol (HAL), risperidone (RIS) and clozapine (CLZ) on the reduction of MTT and exclusion of trypan blue (TBE). Data is measured at 4 different time points (●, 4 h; ■, 24 h; ▲, 48 h and ▼, 72 h), and is corrected for vehicle and background. The lines are all best fits of equation 1 to the data with IC_{50}s given in Fig. 2. Data shown as means ± S.E.M ($n=9$) for each time point.