PLASMA FREE AND TOTAL TRYPTOPHAN : CHRONOPHARMACOLOGICAL EFFECTS OF ANTIDEPRESSANT DRUGS

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It has been reported that depressive illness is associated with disturbances of circadian rhythms (e.g Pflug et al 1976) and it has further been shown that altered 24 hour rhythms of indoles are to be found in both unipolar and bipolar depressive patients (Wirz-Justice 1978): In line with these observations we have presented data showing that antidepressant drugs are capable of modulating the normal diurnal rhythms in tryptophan (TRY) and 5-hydroxytryptamine (5-HT) concentrations in the rat brain (Martin & Redfern 1982). Because we observed greater effects on brain TRY than on brain 5HT rhythms, the influence of antidepressant drugs on diurnal variation in availability of plasma TRY has now been investigated.

Male Wistar rats (University of Bath strain), 150-200g, housed in groups of 6 for 14 days on a 12:12h L:D lighting regimen (lights on 0600h). Imipramine HCl, clomipramine HCl or zimelidine diHCl (200 $mg^{-1}l$) was administered via the drinking water. After 2 or 14 days, groups of animals were killed by decapitation at 0100, 0700, 1300 and 1900 hours and the blood collected into heparnised tubes. Plasma samples were obtained by centrifugation at 2000g for 10 minutes. Free TRY was separated by the method of Bloxham et al (1979) immediately after collection and frozen at -20°C as were samples of whole plasma for estimation of total TRY. Trytophan was determined fluorimetrically by the method of Bloxham & Warren (1974).

As expected, in control animals, plasma levels of both free and total TRY showed a significant diurnal variation, highest levels occurring at 0700h. As can be seen from Table 1, imipramine tended to lower free TRY levels after both 2 and 14 days, resulting in an apparent abolition of the normal rhythm. The effects of clomipramine and zimelidine were less marked after 2 days; after 14 days both drugs significantly increased free TRY levels at 1300h, a result which is consistent with a slowing of the normal rhythm and consequent delay in the appearance of the peak.

Table 1.

		0100		0700		1300		1900	
TREATMENT		FREE	TOTAL	FREE	TOTAL	FREE	TOTAL	FREE	TOTAL
CONTROL		4.27±0.23	21.33±1.09	5.14±0.24	20.52±0.68	3.73±0.35	21.33±1.36	4.07±0.22	16.29±0.52
IMIPRAMINE	2/7	4.07±0.24	17.34±0.77	4.23±0.11	19.27±0.89	4.21±0.26	17.09±1.14	4.07±0.21	18.26±1.10
IMIPRAMINE	14/7	3.61±0.17	23.76±1.49	3.85±0.16	23.07±0.80	3.58±0.11	27.53±1.87	3.40±0.18	22.39±2.15
CLOMIPRAMINE	2/7	3.97±0.18	22.61±0.72	4.03±0.24	23.81±1.81	3.34±0.19	17.40±1.09	2.78±0.30	18.87±1.54
CLOMIPRAMINE	14/7	4.84±0.09	23.64±1.84	5.27±0.16	21.95±1.47	5.4±0.06	18.86±0.17	4.32±0.22	16.76±1.29
ZIMELIDINE	2/7	4.31±0.33	20.85±0.84	5.77±0.18	24.78±1.43	3.46±0.16	14.27±0.53	4.15±0.10	19.52±0.70
ZIMELIDINE	14/7	4.24±0.32	21.77±1.10	5.57±0.34	19.76±1.40	5.68±0.18	21.56±0.94	3.89±0.48	17.19±1.85

concentrations are expressed as $\mu g\ ml^{-1}$ plasma { (mean±s.e.m), (n=4,5 or 6) }

Thus, these results provide additional evidence that the antidepressant drugs studied are capable of attenuating or delaying normal diurnal rhythms, and further suggest that previously reported changes in brain indoleamines may be partly mediated through an action on precursor availability.

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