LACK OF CORRELATION BETWEEN IN-VITRO AND IN-VIVO ESTIMATES OF 5-HT_2 RECEPTOR ANTAGONISM

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Evidence for the existence of a 5-HT receptor sub-type (designated 5-HT_2) first came from radioligand binding studies (Peroutka and Snyder, 1979). Since that time there has been a search for in vivo tests that correlate with the results from the binding studies, but currently there is a lack of agreement. Thus, a significant correlation between 5-HT_2 binding potency and the ability of drugs to antagonise 5-hydroxytryptophan (5-HTP)- induced head twitches in mice has been claimed by Peroutka et al (1981), but this conclusion has been challenged by Middlemiss (1982) who found no such correlation. In the present study an attempt has been made to seek a correlation between the ability of drugs to bind to 5-HT_2 binding sites in vitro and their potency in two in vivo tests which are claimed to measure interactions at 5-HT_2 receptors. A total of 18 drugs were used, which are known to interact with 5-HT receptors, in order to avoid the criticisms levelled at Middlemiss (too few drugs) and Peroutka et al (inappropriate drugs).

In vitro affinity for the 5-HT_2 receptors of rat brain frontal cortex was measured by the ability of antagonists to displace [^{3}H]spiperone from its binding sites according to the method of Middlemiss et al (1980). The potency of the antagonists in vivo was determined by the ability to antagonise 5-HTP-induced head twitches in mice (Corne et al 1963) and fenfluramine-induced hyperthermia in rats (Blackburn et al 1985). Correlations were sought using the negative log of the molar IC_{50} values for the in vitro data and the ED_{50} values (μmoles kg^{-1} s.c.) for the in vivo data. The drugs used were amitriptyline, 2-bromolysergic acid diethylamide (BOL 148), chlorpromazine, cinanserin, clozapine, cyproheptadine, ketanserin, MA1420 (6-acetamido-3-(1-[4-phenyl-piperazino]propyl) 1, 2, 3, 4-tetrahydroquinazoline-2, 4-dione), methergoline, methiothepin, methysergide, mianserin, pipamperone, pirenperone, pizotifen, spiperone, trazadone and trifluorpromazine.

No significant correlation was found between the ability of drugs to displace [^{3}H] spiperone from 5-HT_2 binding sites and their ability to antagonise either 5-HTP-induced head twitches in mice ($r= 0.26$, $P>0.5$) or fenfluramine-induced hyperthermia in rats ($r= -0.27$, $P>0.5$). There was however a significant correlation when the results of the two in vivo models were compared ($r=0.95$, $P<0.0001$).

Thus these results support the findings of Middlemiss (1982) and give a more convincing demonstration of the lack of a correlation between the in vitro and in vivo tests. However it would be unwise to conclude that 5-HT_2 receptors are not involved in the mediation of the effects of 5-HTP and fenfluramine, since ketanserin, which is known to be specific for the 5-HT_2 receptor subtype, was effective in both the in vivo tests. Therefore the lack of a correlation between the in vivo and in vitro data discussed above is likely to have a pharmacokinetic rather than a pharmacological basis. When the influence of the pharmacokinetic variable is reduced (by comparing in vivo with in vivo) then demonstration of a significant correlation is possible.

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