J. Pharm. Pharmacol. 1998, 50 (Supplement): 215

Behavioural evidence in mice of a paradoxical anxiogenic effect of an angiotensin II (AT_1) receptor antagonist

A. G. CRESSWELL AND P. R. GARD

Department of Pharmacy, University of Brighton, Moulsecoomb, Brighton BN2 4GJ

Losartan, a non peptide selective antagonist at the angiotensin, AT_1, receptor, elicits anxiolytic-like responses in mice (Barnes et al, 1990), although these effects are strain dependent (Cambursano et al, 1997). Such findings suggest that the AT_1 receptor, and endogenous angiotensin II, may play a rôle in the genesis of anxiety-like behaviour in mice. The aim of this study was to use the elevated plus maze and burying behaviour to explore the rôle of central angiotensin, and its receptors, in the modulation of anxiety-like behaviour.

The elevated plus-maze consists of an elevated cruciform runway, with arms of 8 x 15 cm. The outer limits of two of the opposing arms are enclose by walls (height 15 cm), but are open-topped. The animal is placed in the centre of the maze and has a natural tendency to move into one of the enclosed arms; anxiolytic drugs increase the amount of time spent on the open runways (Pellow et al, 1985); this test is also claimed to be sensitive to increased anxiety.

Burying behaviour is also a measure of anxiety (Treit, 1985). In this study burying behaviour, sometimes termed defensive burying, was defined as the excessive, repeated movement of the bedding material, in this case saw-dust, by the mice using the front paws. For quantification of burying, groups of 3 mice were placed into a circular arena (diameter 40 cm) containg saw-dust to a depth of 5 cm. The activity of the mice was video recorded and subsequently analysed for each of the 3 mice to give scores for the number of burying episodes, and the amount of time spent burying per 5-minute period.

In the first series of experiments naive male BKW strain mice (25-30g) received losartan (20mg.kg^{-1}), angiotensin II (0.75-1.25mg.kg^{-1}) or vehicle control intraperitoneally after which their behaviour was assessed on the elevated plus-maze at various times; the group size was 6 for all experiments. In comparison to vehicle control, losartan caused a four-fold increase in the amount of time spent on the open arms 15 minutes after drug administration ($p<0.001$) and an eight-fold increase at 30 minutes ($p<0.001$). There was also a four-fold increase in the number of entries onto the open arm at the latter time point ($p<0.001$). Losartan had no significant effect on the total activity of the animals on the maze at either of these time points, nor did it have any significant effect on any parameter when tested 1, 2 or 3 hours after drug administration.

Angiotensin II (1.5mg.kg^{-1}) caused a 60 per cent decrease in the number of entries onto the open arms when tested 1 minute after dosing ($p<0.05$ compared to vehicle control), although at this dose there was also a significant decrease in the total activity on the maze ($p<0.01$). There were no significant effects of the lower doses of angiotensin II.

In the second series of experiments, losartan (20mg.kg^{-1}) paradoxically caused an increase, up to ten-fold, in the number of burying episodes and the amount of time spent burying during the first 15 minutes following drug administration ($p<0.02$, $n=6$ for all groups). This effect of losartan could be totally inhibited by administration of the AT_2 receptor antagonist PD123319 (20mg.kg^{-1}, i.p.) 5 minutes prior to the administration of the losartan. Angiotensin II (1.5mg.kg^{-1}, but not 1.0mg.kg^{-1}) caused a decrease in the episodes and duration of burying during the first 5 minutes post dosing ($p<0.05$, $n=6$ in all cases), although this may reflect the effect of angiotensin on general activity (see results above).

These results confirm the anxiolytic effect of losartan in BKW strain mice but also indicate that losartan elicits an initial, short-lived anxiety-like response. The implications of this finding are unclear but antagonist studies show that it is mediated by the AT_2 receptor, suggesting that antagonism of the AT_1 receptor unmasks a previously unreported AT_2-mediated behavioural response. Attempts to demonstrate an anxiogenic effect of angiotensin II were confounded by the general depressant effects of the peptide.

Barnes, N.M. et al (1990) Neuroreport 1: 15-16
Cambursano, PT et al (1997) J. Pharm. Pharmacol. 49(Suppl. 4): 64
Pellow, S. et al (1985) J. Neurosci. Methods. 14: 149-167
Treit, D. (1985) Neurosci. Biobehav. Rev. 9, :203-222