STRAIN DIFFERENCES IN THE EFFECTS OF ANGIOTENSIN IV ON OBJECT RECOGNITION IN MICE

P.R. Gard and Aikaterini Pavli. School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton BN2 4GJ UK.

Angiotensin type 4 (AT_4) receptors are present in brain areas distinct from those possessing AT_1 and AT_2 receptors and are also an insulin-related amino peptidase known as oxytocinase (Albiston *et al.* 2001). Intracerebroventicular (icv) administration of AT_4 receptor agonists improves memory retention and retrieval in normal rats (eg Wright *et al* 1993) and in rat models of amnesia (eg Wisniewski *et al.*, 1993). If angiotensin IV (Ang IV) analogues are to be developed further, effects on more therapeutically relevant forms of cognitive deficit and routes of administration other than icv need to be studied. The aim of this study was to investigate learning and memory in different strains of mouse and the effects of peripheral administration of Ang IV.

Cognition was assessed using object recognition in which mice are placed into an open field containing two identical objects and allowed to explore for 3 min. One hour later they are again exposed to the same open field and objects for 3 min. After 24h the mice are exposed to the field containing one of the original objects and a novel (different size, shape, colour) object. Time spent exploring each of the objects is recorded over 3 minutes, as is locomotor activity. Learning is quantified as the proportion of time spent exploring the novel object compared with the familiar object (D score).
The effects of Ang IV (0.47mg kg^{-1}, s.c.) administered immediately after the second training trial, was assessed in male CD-1 (25-37g), BKW (17-20g), C57/BL (19-25g) and DBA/2 mice (11-20g) compared with saline controls.
The results, shown in the table, indicated that there was a significant strain difference in object recognition (p=0.004, ANOVA). Ang IV significantly increased object recognition in DBA/2 (p=0.01, Student's t-test), but had no significant effect in the other three strains.

Strain	Object Recognition D Score ($\pm$ sem)	
	Saline	Angiotensin IV
C57/BL	0.49 ± 0.04 (n=10)	0.46 ± 0.08 (n=10)
CD-1	0.34 ± 0.06 (n=9)	0.26 ± 0.13 (n=10)
BKW	0.19 ± 0.04 (n=10)	0.24 ± 0.12 (n=10)
DBA/2	0.10 ± 0.06 (n=10)	0.39 ± 0.09 (n=10)

Table: Object recognition in saline- and Angiotensin IV-treated mice.

There was also a significant strain difference in locomotor activity counts during the test trial (BKW: 115 ± 5 (n=10); C57/BL: 85 ± 9 (n=10); DBA/2: 82 ± 8 (n=10); CD-1: 70 ± 5 (n=9); p=0.001, ANOVA). Ang IV caused a significant increase in only BKW and CD strains (144 ± 6 and 106 ± 10 respectively; $p<0.005$).
These results indicate that Ang IV improves learning and memory in a mouse strain with inherently poor cognition. It also increases locomotor activity, but in strains different from that in which there is a cognitive-enhancing effect which suggests that the cognitive and locomotor effects have different mechanisms. Importantly the results show that Ang IV is effective when administered peripherally.

Albiston *et al.* (2001) *J. Biol. Chem*. **276**: 48623-48626.
Wright *et al.* (1993) *Brain Res. Bull*. **32**: 497-502.
Wisniewski *et a.l* (1993) *Pol. J. Pharmacol*. **45**:23-29.