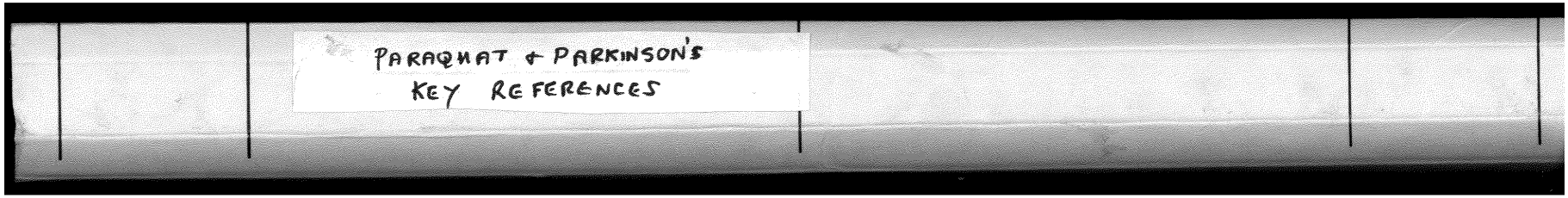

8. Suppression of paraquat-induced wet dog shakes by nitric oxide synthase inhibitors in rats
Hara et al (2000) Life sciences 66, 189-194.

This paper confirm a previous report by this group and observation made in our own laboratory (MF and EAL) that at high systemic doses paraquat causes wet dog shakes in rats. These effects are seen around the time of peak blood and brain levels of paraquat. They are seen generally at high dose above the median lethal dose, these authors used 70mg/kg sc.

The effect is shown to be partially blocked by NO synthase inhibitors and reversed by naloxone but not L-arginine suggesting the effect is mediated via central opioid receptors.

A high dose phenomenon, but it does show that at very high blood levels some paraquat can enter the brain and produce a behavioural change in rats.

EAL/3Aug 00

13 Paraquat: a useful tool for the in vivo study of mechanisms of neuronal cell death
Corasaniti et al, (1998) Pharmacol. Toxicol. 83, 1-7

This is a review of the paper by the Italian group on the neurotoxic potential of paraquat and contains some of the information that we have refuted in our published work.
They again make a strong play that paraquat **may be** linked to Parkinson's disease. They cite their work showing that paraquat is very neurotoxic when injected directly into the brain and make the point that it is not selective to the dopaminergic nigro-stratial system. This is not surprising to me as when injected you will damage cells around the site of injection and paraquat will be able to redox cycle and cause neuronal cell loss.
They discuss their work when paraquat is given systemically and still causes some neurobehavioral effects and "brain damage" We agree that a small amount of a systemic doses can cross the blood brain barrier but at realistic oral doses it does not lead to brain damage or any marked behavioural effects.
They refer to their more recent work showing that injection of paraquat into the hippocampus will cause neuronal cell apoptosis and are advocating its use as a model to study neuronal cell death.

Overall, not a lot of new findings of concern, but it raises the profile of the neurotoxic effects of paraquat, as seen at high doses and non relevant routes of exposure. Overall there is not doubt that some paraquat can enter the brain of rats, probably by routes which lack a blood brain barrier. This will continue to give us problems over the coming years as we cannot refute it categorically. A pharmacodynamic model of human versus rodent is probably one of the best approaches, this will require blood level measurements in spray workers to put into any model to help assess the risk. Again the Parkinson link will not diminish, we are stuck with it.!
EAL/3Aug 00

PAPER NOT HELD.

KEIKO. (35)
1999

Keiko *et al*., (1999) Paraquat is carried through the blood brain barrier by a certain amino acid transporter. *Jap J Forensic Toxicol.* **17**, 136-137

Just read the abstract, the full paper all 2 pages is in Japanese.

Seems very interesting.

The authors used microdialysis to show that paraquat enters the rat brain, not sure at what time after dosing 20mg/kg ip???. The fact that they claim to not be able to detect MPP^+ but can paraquat is worrying and implies selective entry via a transporter?? of paraquat.

The amino acid valine reduces brain levels of paraquat. Not clear to me why paraquat should enter via a neutral amino acid transport system?? No data provided.

The finding is sufficiently important that we should be following this up, EAL will try and do some studies in rats later in the year.

Ted Lock. 14 Jan 2000

Kubo *et al* (1999) Immunohistochemical studies on paraquat-induced damage to neuronal and glial cells in rat hippocampus. *Acta Histochem. Cytochem.* **32,** 373-376.

This paper reports immunocytochemical studies in rat brain from animals doses with paraquat. The authors exposed rats to 25, 50 or 100mg/kg paraquat given ip and killed the animals 24hr later. The brains were perfuse-fixed and sections of the hippocampus stained for microtubular associated protein (MAP-2), a neuronal cell marker and Glial fibrillary acidic protein (GFAP) a marker of glial cells.
They found a decrease in antibody reactivity with the MAP-2 antibody in the CA ½ region of the hippocampus, but not in the CA3 region at 25 and 50mg/kg paraquat with a smaller effect at 100mg/kg. GFAP expression as judged by cross reactivity with the antibody was reduced at all doses.
The authors conclude that paraquat administration to rats can lead to neuronal and glial cell loss.

COMMENTS

- very high doses of paraquat, MLD and above were used. I am surprised that the animals at 100mg/kg survived for 24h
- they did perfuse-fix the tissue which is good and the antibodies seemed to work, although the quality of the photocopy of the Figures limits comment. I will send a copy to John Foster for comments on the techniques used.
- it is puzzling why the response to MAP-2 at 100mg/kg paraquat "appears" to recover
- reduced cross reactivity with antibodies does not necessarily mean that the cells are lost.
- it would be useful to know what happens at doses lower than 25mg/kg ip, how low down the dose response curve do these changes occur.
- This paper adds to previous work by the Japanese showing that paraquat appears to localise in brain endothelial cells and glial cells, but it was not found in neuronal cells, which does not fix with this work!!.

Overall a high dose effect but this work is adding to the mounting number of paper exploring and reporting CNS effects of paraquat in experimental animals.