ABSTRACT

Pharmacological Studies of A Muscarinic Alkaloid

Isolated from ***Abutilon trisulcatum***

Maxine Deborah Gossell-Willliams

The renewed interest in plants as sources of new and cheaper medicinal products, led to the investigation of *Abutilon trisulcatum (*anglenstem Indian Mallow) to identify and evaluate the pharmacological potential of alkaloids detected in this plant. Preliminary screening of an aqueous alkaloidal extract showed no signs of acute toxicity, but produced a fall in rat blood pressure. It was assumed the alkaloid detected was responsible for the hypotensive activity of *Abutilon trisulcatum* and therefore this action was used initially to guide the chemical isolation procedures, which produced two alkaloidal extracts, TA and ATRIS. The hypotensive effect was only produced by ATRIS and was determine to involve activation of cholinergic receptors. This was further confirmed using in vitro experiments. These in vitro experiments showed that ATRIS was an agonist of muscarinic cholinergic receptors and they also indicated that ATRIS did not have the same potency for all the major muscarinic receptor subtypes. ATRIS did not activate nicotinic cholinergic receptors, at least not at the concentrations used.

In vitro procedures were then used in this "activity directed' protocol to further isolate the alkaloid present in ATRIS. Further purification of ATRIS lead to the isolation of the chloride salt of a quaternary alkaloid, ALKSII. ALKSII showed similar chemical properties as ATRIS and in vitro testing also indicated that it exhibited muscarinic activity. Recrystalization of ALKSII produced ALKSIIA, which was identified by chemical assays to be choline. The potency of ALKSIIA on the major muscarinic receptors was investigated in isolated preparations with M_1, M_2 and M_3 muscarinic receptor subtypes, using standard agonist and antagonist of these receptors. The agonist potency of ALKSIIA was determined to be greatest for M_1 and it was least for M_2 muscarinic receptors.

Chemical and pharmacological comparisons confirmed ALKSIIA to be choline. Choline is an essential micronutrient, which is a precursor for the synthesis of acetylcholine, a neurotransmitter that is important for the proper functioning of memory processes of the brain. *Abutilon trisulcatum* may therefore be a source of choline and thus provide compounds useful as "nutraceuticals" which serve to maintain memory functions and prevent development of memory disorders. This therapeutic potential was investigated with an aqueous extract from *Abutilon trisulcatum* and commercially available choline chloride (as ALKSIIA) to determine their effects on intermediate long-term memory in rats. The memory experiments involved training rats in "one-way shuttle box passive avoidance" and " simultaneous brightness discrimination

with passive avoidance" paradigms. From these results it was evident that two weeks of daily dosing with an aqueous extract of *Abutilon trisulcatum* and choline chloride improved intermediate long-memory in rats. This therapeutic potential of *Abutilon trisulcatum* may be attributed to its choline content. *Abutilon trisulcatum* may therefore be useful therapeutically for prevention and the treatment of memory disorders such as Alzheimer's disease.

Keywords: *Abutilon trisulcatum*, alkaloid, activity-directed, muscarinic agonist, receptor selectivity, Schild analysis, choline, nutraceutical, functional food, passive avoidance, intermediate long-term memory.