# THE PREJUNCTIONAL $\alpha_2$-ADRENOCEPTOR ANTAGONIST ACTIVITY OF PYREXTRAMINE

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Alpha-adrenoceptors have a widespread distribution and are involved in the mode of action of many clinically important groups of drugs. Their subclassification into $alpha_1$ and $alpha_2$ subtypes has allowed a greater degree of selectivity in the design of drugs. The possibility of further subclassification of alpha adrenoceptors has been prompted by research into the differential activity of imidazolines and β-phenethylamines on alpha receptors (Ruffolo et al, 1983). A parallel study on this hypothesis was carried out by Mottram & Thakar (1984) using a non-competitive alpha antagonist, benextramine. Results showed that benextramine was more effective in blocking alpha agonists of the imidazoline type rather than the β-phenethylamine type. Experiments were somewhat hampered by the concomitant muscarinic receptor blocking activity of benextramine.

Recently Brasili et al (1984) have reported on the irreversible alpha - adrenoceptor blocking activity of a related compound, Pyrextramine. The present study was therefore undertaken to investigate the blocking action of pyrextramine on $alpha_2$-adrenoceptors to determine its selectivity of action and to establish whether a differential blockade of imidazolines and β-phenethylamines occurred with this drug.

Studies were carried out on the prejunctional $alpha_2$-adrenoceptor mediated responses of field stimulated guinea pig ileum. Tissues were bathed in Kreb's solution containing 3 μM cocaine, 1 μM propranolol and 0.3 μM prazosin to inhibit neuronal uptake and to block beta and $alpha_1$-adrenoceptors respectively. Field stimulation, generated by Grass Stimulators, was applied to the tissues using square wave pulses of 3 m sec duration, submaximal voltages and a frequency of 0.1Hz. Isometric contractions were recorded on Lectromed recorders. Cumulative dose response curves to the agonists B-HT920, an imidazoline-like compound (Mottram, 1983) and α-methyl noradrenaline, a β-phenethylamine, were recorded. Varying concentrations of pyrextramine (10nM to 3 μM) were used to inhibit these agonists using short (5 mins) or long (30 mins) exposure times. Reversibility of blockade was tested by repeating cumulative dose-response curves after several washings of the tissue.

Results showed that pyrextramine is effective in blocking $alpha_2$-adrenoceptors in addition to its $alpha_1$ blocking activity previously reported. A longer exposure was required for the development of a full antagonist activity with associated non-competitive irreversible characteristics. Antagonism of B-HT920 began with a 30 min exposure to 30 nM Pyrextramine. Increasing concentrations produced a dose dependant blockade which was 90% complete at a concentration of 0.3 μM Pyrextramine. This same dose range and time of exposure did not produce the same degree of antagonism against α-methyl noradrenaline. Comparison with its precursor, benextramine shows that pyrextramine requires a ten-fold decrease in concentration to achieve equivalent blockade of $alpha_2$-adrenoceptors.

Conversely the depression of the twitch response, seen with benextramine, due to muscarinic blocking activity (Mottram & Thakar, 1984) was virtually absent up to 0.3 μM pyrextramine.

Pyrextramine is therefore a more selective and more potent alpha blocker than benextramine. Once again differential antagonist activity against imidazoline-like and β-phenethylamine-like agaonists suggests that alpha adrenoceptors may need further subclassification beyond the present $alpha_1/alpha_2$ subdivision.

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