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SYNTHESIS AND PHARMACOLOGY OF N-(4-DIETHYLAMINO-2-BUTYNYL)-SUCCINIMIDE (DKJ 21), A NEW CENTRAL ANTICHOLINERGIC AGENT

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OXOTREMORINE, the metabolic oxidation product of tremorine[1,2], has been shown to exert a variety of profound effects on the central nervous system[3,4,5], some of which appear analogous to extrapyramidal motor disturbances seen clinically. Its effects are antagonized by many agents of therapeutic value in these disorders, and both tremorine and oxotremorine have found wide use as screening agents for this type of activity. While the principle pharmacological properties of oxotremorine appear to be associated with its intense muscarinic activity, its actions upon the central nervous system are more marked than those of other muscarinic tertiary amines such as arecoline, pilocarpine and aceclidine. This relative specificity has led to the synthesis of structural analogues of oxotremorine in a search for blocking agents of similar specificity which might be of clinical value as central anticholinergic agents. Among several types of compounds studied, one class appeared to be of special interest, namely, 1-(4-dialkylamino-2-butynyl)-succinimides. This report is concerned with the synthesis and pharmacological properties of one of these compounds, N-(4-diethylamino-2-butynyl)-succinimide (DKJ 21), which was selected on the basis of its potency in blocking the motor effects of oxotremorine relative to its in vivo mydriatic activity. Detailed reports of this and other analogues will be published subsequently.

Methods

DKJ 21 was prepared by treating the sodium salt of succinimide with propargyl bromide. The resulting N-propargylsuccinimide was submitted to the Mannich reaction with formaldehyde and diethylamine in boiling dioxane in the presence of cuprous chloride. The resulting N-(4-diethylamino-2-butynyl)-succinimide was an oil which was isolated and purified as the hydrochloride, m.p. 183-183.5°C after recrystallization from ethanol. The compound was also prepared by an alternative method, in which 4-diethylamino-2-butynylamine was treated with succinic anhydride to give N-(4-diethylamino-2-butynyl)-succinamic acid, which was then cyclized with the aid of acetic anhydride and anhydrous sodium acetate to give DKJ 21. The reactions used are illustrated in Fig. 1.

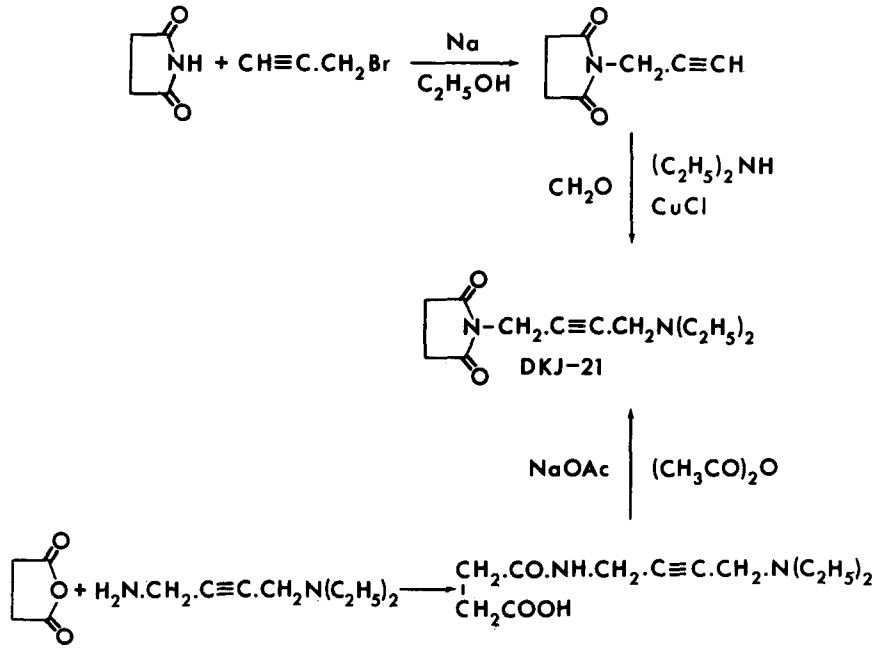

FIG. 1

Reaction sequence for synthesis of DKJ 21.

Mydriatic activity and antagonism of the motor effects of oxotremorine were assessed following intraperitoneal injection of graded doses into groups

of five mice each. Pupil size was measured 20 min. after injection under constant lighting conditions, using a binocular microscope fitted with a calibrated eyepiece, and compared with a similar measurement made immediately before injection. Oxotremorine (100 µg/kg) was then injected intravenously into both control and premedicated groups, and the effects were recorded by a visual grading procedure[6]. Standard procedures were used for the other experiments described, except where noted in the text.

Results

Fig. 2 shows the mydriatic and tremorolytic effects of DKJ 21 as a function of dose in comparison with atropine. Significant pupillary dilation was seen following a dose of atropine which failed to influence the response to oxotremorine; in contrast, an essentially complete blockade of the motor effects of oxotremorine could be produced by a dose of DKJ 21 which left the pupil size unchanged. Quantitatively similar results were obtained when arecoline (300 µg/kg IV) was used in place of oxotremorine. The anticholinergic basis of this blockade was confirmed by the finding that the lethal toxicity of physostigmine in mice (1 mg/kg IP) was reduced by DKJ 21 (50 mg/kg IP) from 13/20 to 1/20, a highly significant difference ($P<.01$ percent).

This evidence of a selective central anticholinergic action was seen also in larger animals such as cats and rabbits, and was particularly marked in cats, which show a characteristic rage response in addition to the motor disturbances after oxotremorine[3,7]. Premedication with DKJ 21 (50-100 mg/kg IP) completely prevented or reversed the tremor, ataxia, rigidity and rage seen after injection of oxotremorine (300 µg/kg IP) or arecoline (500 µg/kg IP); peripheral parasympathetic effects such as salivation, lacrimation, defecation and urination were substantially unaltered. Simultaneous premedication with both methantheline (2-5 mg/kg IP) and DKJ 21 (50-100 mg/kg IP) prevented or reversed both the central and peripheral effects of oxotremorine; atropine (2 mg/kg IP) also blocked both types of effect. Similarly, the depressor

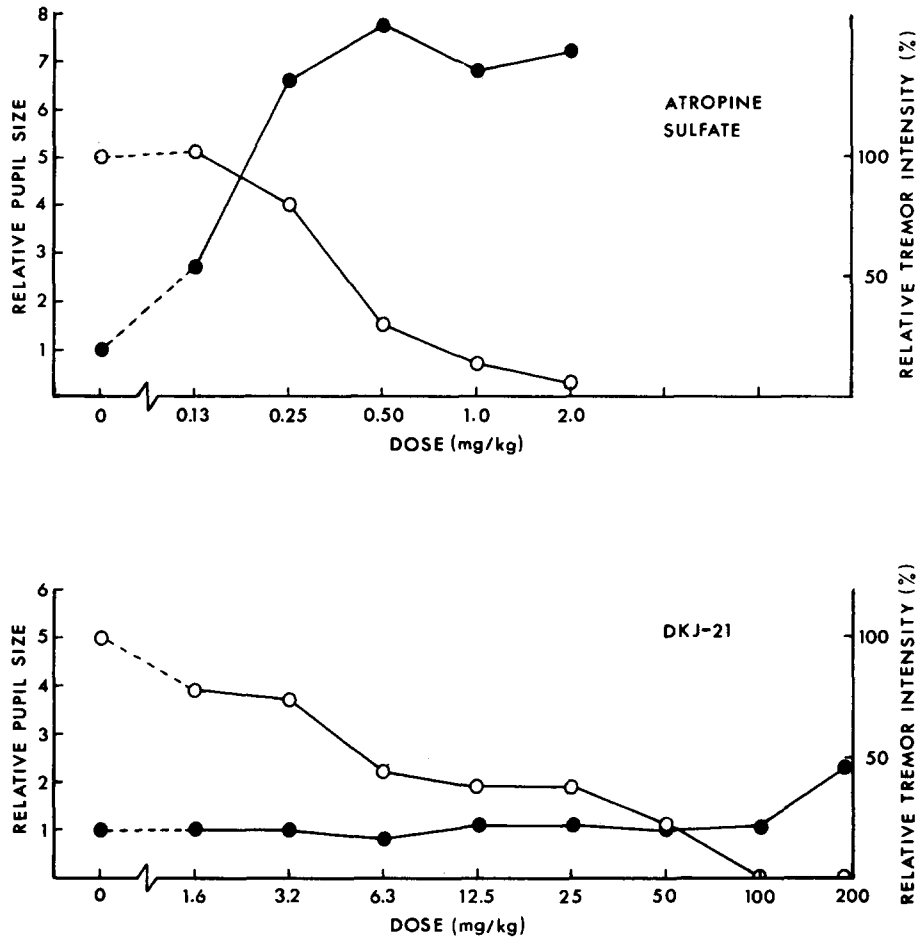

FIG. 2

Effect of atropine sulfate and DKJ 21 on pupil size ( ) and tremor intensity ( ) following oxotremorine (100 µg/kg IV) in mice. Pupil size is referred to preinjection diameter; tremor intensity was graded visually and is referred to that seen in unpremedicated control mice. Each point represents the mean response of five mice.

effect of acetylcholine, oxotremorine or carbachol in anesthetized cats and dogs was completely unchanged by previous doses of up to 50 mg/kg DKJ 21 intravenously.

INFLUENCE OF ATROPINE AND DKJ-21 ON PRESSOR/DEPRESSOR EFFECTS OF McN-A-343

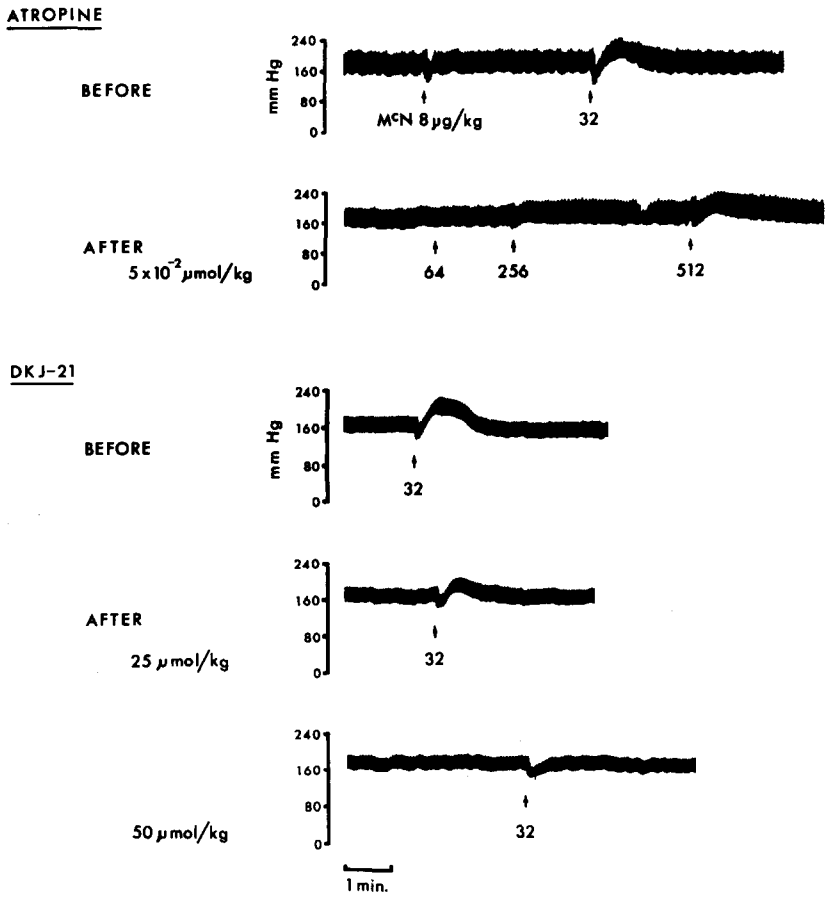

FIG. 3

Influence of atropine and of DKJ 21 on the pressor and depressor effects of McN-A-343 in anesthetized cats. Figures below the tracing in each case show the dose of McN-A-343 injected intravenously. Each antagonist was tested on a separate cat.

The lack of peripheral parasympatholytic actions of DKJ 21 was confirmed on isolated strips of guinea pig ileum. A concentration of 10^{-5} M was required to reduce the response to a double dose of acetylcholine to that

produced by a single dose in the absence of the antagonist; the corresponding concentration for atropine was 2.6×10^{-10} M. Atropine was therefore 40,000 times as potent as DKJ 21 on this preparation.

In contrast to these results, DKJ 21 was found in anesthetized cats to block selectively the pressor response to McN-A-343, a related compound which stimulates sympathetic ganglia and can be specifically blocked by atropine[8], suggesting the involvement of a type of muscarinic receptor. Almost complete blockade of the pressor response to McN-A-343 (32 µg/kg IV) was consistently obtained with 5-10 mg/kg DKJ 21. The secondary depressor response, which probably depends upon the peripheral muscarinic activity of McN-A-343, was unaltered (Fig. 3). In conformity with these results, DKJ 21 (50 µg intra-arterially) completely blocked the response of the nictitating membrane to the close arterial injection of McN-A-343, while leaving the response to DMPP unaltered.

Summary and Conclusions

Evidence has been presented which leads to the conclusion that DKJ 21 is an anticholinergic agent with a marked selectivity for the central nervous system. It also appears to block the stimulant effects of McN-A-343 on sympathetic ganglia, suggesting that these may be more closely allied to muscarinic receptors in the central nervous system than to those occurring peripherally.

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