SOME ANTAGONISTS OF ATROPINE-LIKE PSYCHOTOMIMETICS

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The peripheral pharmacological effects of an anti-acetylcholine psychotomimetic drug, ethylpiperidylcyclopentylphenyl glycolate hydrochloride (JB-329) were found to be essentially similar to those of atropine. Both drugs inhibited parasympathetic effects and acetylcholine responses and produced potentiation of the pressor responses to adrenaline and noradrenaline. The compound tetrahydroaminoacridine, shown to be an antagonist of JB-329, was studied and its actions were compared with those of other cholinesterase inhibitors. Certain glycolic acid derivatives, some of which have been shown to antagonise the effects of JB-329, were also studied and their pharmacology and interactions are presented. The mode of action of the antagonists are discussed.

Psychotomimetic effects have been produced by some 3-*N*-substituted piperidyl benzilates in man (Abood, Ostfield and Biel, 1958, 1959; Ostfield, Abood and Mercus, 1958; Pfeiffer and others, 1959). One such compound, JB-329 (*N*-ethyl-3-piperidylcyclopentylphenyl glycolate hydrochloride, Ditran), produces clinical effects simulating some aspects of psychosis more closely than either LSD or mescaline (Gershon and Olariu, 1960; Abood and others, 1958). Behavioural disturbance is also produced in experimental animals (Abood and others, 1959; Biel and others 1961). JB-329 has atropine-like effects in man and animals, an activity demonstrated in the isolated ileum and colon of the rat, and the frog rectus abdominus muscle preparation (Biel and others, 1962).

Atropine in the normal clinical dose has little effect on the central nervous system (Drill, 1958; Goodman and Gilman, 1955) although toxic doses cause hallucinations and disorientation. In large doses it produces behavioural disturbances in animals similar to those seen with JB-329 (Goldenberg, 1957; White and others, 1961; Bell and others, 1963).

The first reported antagonism of the JB-329 syndrome was by Gershon (1960) using 1,2,3,4-tetrahydro-5-aminoacridine (THA). This was found to be an antidote for both the central and peripheral effects of JB-329 in man. THA has marked anticholinesterase activity (Shaw and Bentley, 1953), as well as inhibiting choline acetylase (de la Lande, 1956). Antagonism of the behavioural effects of JB-329 in dogs has been produced with THA and a new series of glycolic acid derivatives (Bell and others, 1963). These compounds significantly reduced the duration of the JB-329 effects on behaviour.

Because of the interest in the atropine-like psychotomimetics and their antagonists it was decided to compare and contrast the actions of JB-329 and atropine, and to investigate the pharmacology of their antagonists.

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To determine the pharmacological basis of the antagonism, the anti-cholinesterase drugs physostigmine, neostigmine and dyflos (DFP) were also used.

EXPERIMENTAL METHODS

Conscious dogs were used to observe behavioural and pharmacological effects. Cardiovascular effects were measured in a manner similar to that described by Gershon and Lang (1962). Dogs were surgically prepared beforehand with exteriorised carotid arteries. Arterial pressure was then measured with a Statham transducer using an Offner dynograph recorder. Electrocardiogram, heart rate, salivation, pupillary size and response as well as behavioural changes were also recorded. All drugs were given by intravenous injection using an indwelling polyethylene cannula in the external jugular vein.

Blood pressures from anaesthetised dogs and cats were recorded from carotid or femoral arteries as described above or sometimes with a mercury manometer and kymograph. Drugs were given by intravenous injection; the anaesthetic was normally pentobarbitone or occasionally chloralose.

In the studies on male volunteers, the procedure was that described by Holmberg and Gershon (1961). Intravenous injections of the test drugs were given through indwelling cannulae. During the whole test procedure the ECG was recorded continuously and blood pressure was taken by auscultation every 30 sec.

Isolated strips of fundus from the rat stomach (Vane, 1957) were used to record the effect of the drugs on contractions produced by 5-hydroxytryptamine (5-HT) 30–60 ng.

JB-329 was used in varying doses and its effects were compared and contrasted with those of atropine sulphate. The antagonists were THA, and several members of the series of glycolic acid derivatives (*p*-phenylmandelic acid; 2- and 3-phenanthrylglycolic acids; phenoxymandelic acid) used by Bell and others (1963). Anticholinesterase compounds neostigmine methyl sulphate, physostigmine salicylate and dyflos were also used.

The compounds adrenaline tartrate, noradrenaline bitartrate, acetylchlorine chloride, histamine acid phosphate and 5-HT creatinine sulphate were used to elucidate the pharmacology of the various compounds.

RESULTS

Pharmacology of JB-329 and atropine

In 14 experiments with conscious dogs, JB-329 (0·5 mg./kg. i.v.) produced an increase in both systolic and diastolic blood pressure (average increase 15/20 mm. Hg) and a simultaneous increase in heart rate (120 beats/ min. increase). A gradual return to normal followed and after 4–5 hr. the blood pressure was at control levels although the heart rate was still higher than the control. Administration of JB-329 (0·5 mg./kg. s.c. daily for 7 days) produced no significant effect on blood pressure or heart rate.

TABLE I

MEAN BLOOD PRESSURE RESPONSES BEFORE AND AFTER JB-329 (0·5 MG./KG.) AND ATROPINE SULPHATE (0·5 MG./KG.)

The baseline indicates the basal blood pressure. Change is calculated as the rise or fall in blood pressure to the peak of response

	Before JB-329		After JB-329		Before atropine		After atropine	
	Baseline ±s.e.	Change ±s.e.	Baseline ±s.e.	Change ±s.e.	Baseline ±s.e.	Change ±s.e.	Baseline ±s.e.	Change ±s.e.
A. Conscious dogs—								
Drug alone	118 ± 7·9	—	118 ± 7·9	+20 ± 3·7	109 ± 5·3	—	109 ± 5·3	+22 ± 6·8
Adrenaline 1 μg./kg.	115 ± 5·3	+38 ± 4·5	125 ± 5·5	+65 ± 5·3	110 ± 3·5	+41 ± 3·8	117 ± 3·9	+95 ± 9·9
Noradrenaline 1 μg./kg.	115 ± 5·7	+38 ± 6·4	129 ± 5·5	+71 ± 7·1	113 ± 4·5	+50 ± 10·5	119 ± 4·9	+105 ± 17·5
Acetylcholine 0·5 μg./kg.	117 ± 4·5	−27 ± 3·7	126 ± 3·7	−3·5 ± 2·4	111 ± 1·5	−28 ± 10·7	123 ± 7·7	−9 ± 5·8
B. Anaesthetised cats—								
Drug alone	12·2 ± 16·0	—	12·2 ± 16·0	−3·1 ± 4·2	*155	+20	—	—
					145	−30	—	—
Adrenaline 2 μg./kg.	138 ± 17·2	+32 ± 5·6	124 ± 15·7	+46 ± 8·0	150	+35	+165	+55
					150	+25	125	+60
Noradrenaline 2 μg./kg.	142 ± 17·5	+49 ± 6·1	217 ± 14·5	+65 ± 7·1	160	+75	160	+110
					150	+35	125	+45
Acetylcholine 0·2 μg./kg.	101 ± 11·8	−37 ± 5·4	90 ± 12·2	0 ± 0	170	−80	155	0
					140	−65	125	0

* Results for atropine are actual recordings in two experiments.

TABLE II

ANTAGONISM BY THA OF THE EFFECTS OF JB-329 ON THE RESPONSES OF THE CATECHOLAMINES AND ACETYLCHOLINE

	Response to noradrenaline 1 μg./kg. in mm. Hg			Response to adrenaline 1 μg./kg. in mm. Hg			Response to acetylcholine 0·5 μg./kg. in mm. Hg		
Dogs	Control	After JB-329 0·5 mg./kg.	After THA 1 mg./kg.	Control	After JB-329 0·5 mg./kg.	After THA 1 mg./kg.	Control	After JB-329 0·5 mg./kg.	After THA 1 mg./kg.
1	+27·5	+37·5	+15	+25	+40	+22·5	−10	0	−12·5
2	+37·5	+85	+45	+32·5	+85	+40	−17·5	0	−5
3	+27·5	+37·5	+20	+35	+45	+17·5	−27·5	0	0
4	+57·5	+65	+42·5	+42·5	+57·5	+37·5	−37·5	0	−22·5
5	—	—	—	—	—	—	−15	0	−20

Tolerance to the autonomic effects of JB-329 with chronic daily medication in man was demonstrated by Gershon and Olariu (1960).

Atropine (0·5 mg./kg. i.v. 4 dogs) produced increases in both systolic and diastolic blood pressures as well as tachycardia of the same degree as JB-329. Autonomic changes with both drugs included inhibition of salivation and dilatation of the pupils with marked slowing of the response to light. The hypotensive effect of acetylcholine was inhibited by both JB-329 and atropine in anaesthetised and conscious animals. Both JB-329 and atropine produced potentiation of the pressor responses to adrenaline and noradrenaline (Table I); these pressor responses were even doubled in some dogs.

In anaesthetised cats and dogs the potentiation was less, but did occur. JB-329 and atropine had little action on the effects of histamine 0·5 μg./kg. or 5-HT 5–10 μg./kg. on the blood pressure in conscious dogs. In anaesthetised cats, the primary sharp fall in blood pressure produced by 5-HT 5–10 μg./kg. was inhibited by JB-329 and atropine. This primary fall due to 5-HT is probably a vagal effect (Page, 1952) so that this observation does not necessarily indicate anti-5-HT activity. In isolated strips of fundus from the rat stomach, JB-329 and atropine exhibited anti-5-HT activity only in concentrations about 5×10^{-4} g./ml.

JB-329 (0·15 mg./kg. i.v.) and atropine (0·03 mg./kg. i.v.) were given to three men. In each, a rise in blood pressure and tachycardia occurred after both drugs. Although the increased blood pressure masked the results, the control pressor responses to adrenaline and noradrenaline were found to be potentiated by JB-329 and atropine when the peaks of the blood pressure rises were measured. The depressor response to methacholine chloride was inhibited by both drugs. The response varied between subjects, but each individual responded similarly to both drugs.

Pharmacology of the Antagonists

Tetrahydroaminacrine hydrochloride (THA). In four conscious dogs, THA, 1 mg./kg. i.v., produced no significant change in blood pressure or heart rate, but effects like salivation, vomiting, diarrhoea and twitching were occasionally observed.

In six anaesthetised cats, there was a fall in blood pressure of 30–40 mm.Hg, after which there was a return to normal. In four animals, a secondary rise to approximately 30 mm.Hg above the original level occurred. In two other cats, only the rise in blood pressure occurred. THA produced no apparent modification of the reflex rise in blood pressure occurring after occlusion of the carotid arteries.

The depressor response to acetylcholine 0·2–0·5 μg./kg. was increased in magnitude and duration after THA in conscious and anaesthetised preparations, in keeping with the known anticholinesterase action of the compound.

Variable modifications occurred in the blood pressure responses to injected adrenaline and noradrenaline after THA. In conscious dogs, THA, 1 mg./kg., produced no significant effect on the responses. However,

in anaesthetised cats there sometimes occurred inhibition or reversal of the blood pressure responses.

The diphasic response produced by adrenaline and the magnitude of the noradrenaline-induced rise in blood pressure in the anaesthetised cat, varied with the blood pressure level or the depth of anaesthesia or both

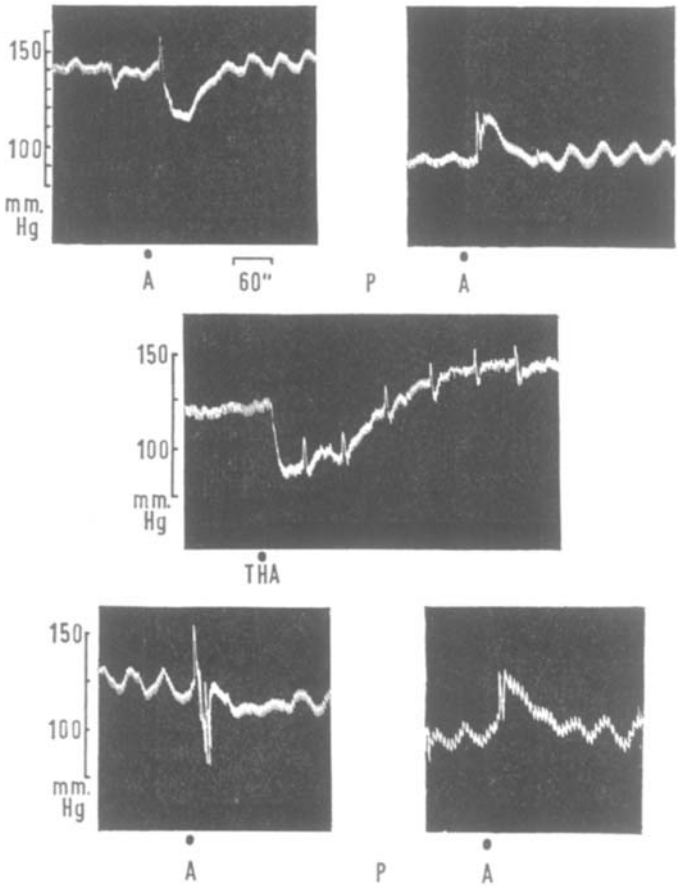

FIG. 1. Blood pressure record in a cat anaesthetised by pentobarbitone 40 mg./kg. i.p. A = i.v. injection of adrenaline 10 μg. THA = i.v. injection of THA 1 mg./kg. P = i.p. injection of pentobarbitone 15 mg./kg. with an interval of 10 min. between the traces. The upper record shows the responses to adrenaline as affected by pentobarbitone-induced changes in depth of anaesthesia and blood pressure base-line before THA injection. The middle record shows the effect of THA on blood pressure. The lower record shows the responses to adrenaline after THA.

(Fig. 1). It appeared from the results that the inconsistent inhibition and reversal of adrenaline and noradrenaline responses produced by THA were due to modifications of the basal blood pressure and depth of anaesthesia. Thus, when the blood pressure was raised or the anaesthesia lightened after THA, then the pressor response to the catecholamines was inhibited

and the depressor response to adrenaline was made apparent or exaggerated. With the dosage of THA used (1 mg./kg.), the experiments on the conscious dog show that no true anti-adrenaline action occurred. Responses to histamine and 5-HT were not significantly affected in the conscious or anaesthetised preparations.

p-*Phenylmandelic acid.* In eight conscious dogs this compound (5 mg./kg. i.v.), an active antagonist of the JB-329-induced syndrome (Bell and others, 1963), produced variable and inconsistent effects on blood pressure. Heart rate was affected only when changes in blood pressure initiated reflex responses. Chronic administration of the same dose daily for one week also produced no significant effects in five dogs. A gradual increase in blood pressure (average value 15–20 mm.Hg) was apparent in seven of eight anaesthetised cats (a similar response was seen with THA). However, no significant changes occurred in the heart rates of these animals.

In the conscious dogs, no apparent behavioural change was seen or autonomic functions affected with either acute or chronic administration of *p*-phenylmandelic acid.

The only modifications of neurohumoral responses on blood pressure were an increase in magnitude and duration of the depressor effect of acetylcholine 0·2 μg./kg. and the secondary fall after adrenaline 2 μg./kg. in anaesthetised cats. There was no effect on 5-HT-induced contraction of rat stomach muscle strips.

2-*Phenanthrylglycolic acid,* 3-*phenanthrylglycolic acid and phenoxymandelic acid.* The first two compounds (effective antagonists of the JB-329-induced syndrome) and the third compound (ineffective against JB-329, Bell and others, 1963) in single doses of 10 mg./kg. i.v. in anaesthetised cats produced increases in blood pressure of approximately 20 mm.Hg. The depressor response to acetylcholine 0·2 μg./kg. was potentiated in magnitude and duration by the compounds, while that to histamine was antagonised by both 2- and 3-phenanthrylglycolic acids but not by phenoxymandelic acid. The 3-phenanthrylglycolic acid appeared to have the greater antihistamine effect and completely abolished the fall in blood pressure induced by histamine 0·2 μg./kg. No significant effects were produced on the responses produced by the other neurohumors or the reflex rise in blood pressure after occlusion of the carotid arteries.

Interactions between Psychotogens and Antagonists

JB-329 and THA. The cardiovascular changes produced by JB-329, 0·5 mg./kg., were antagonised by THA, 1 mg./kg., in five conscious dogs. The blood pressure was lowered, pulse pressure was increased and tachycardia was lessened. In addition the autonomic changes produced by the anticholinergic actions of JB-329 were antagonised. The potentiated pressor responses to injected adrenaline and noradrenaline, 2 μg./kg., were returned to control values and in some cases were even reduced. Blockade of the response to acetylcholine 0·5 μg./kg. was partially or completely antagonised in four of the five dogs (Table II).

In anaesthetised cats, the results were similar except that the blood pressure was increased slightly by THA after JB-329.

Overall results indicated complete antagonism by THA of the effects of JB-329.

JB-329 and other anticholinesterases. Neostigmine methyl sulphate, 0·03 mg./kg., given before or after JB-329 partly antagonised the potentiation of the responses to adrenaline and noradrenaline and the blockade of responses to acetylcholine resulting from JB-329.

In both conscious and anaesthetised animals, a larger dose of neostigmine, 0·05 mg./kg., given after JB-329, produced a complete antagonism of all peripheral pharmacological and autonomic changes in the same way as did THA.

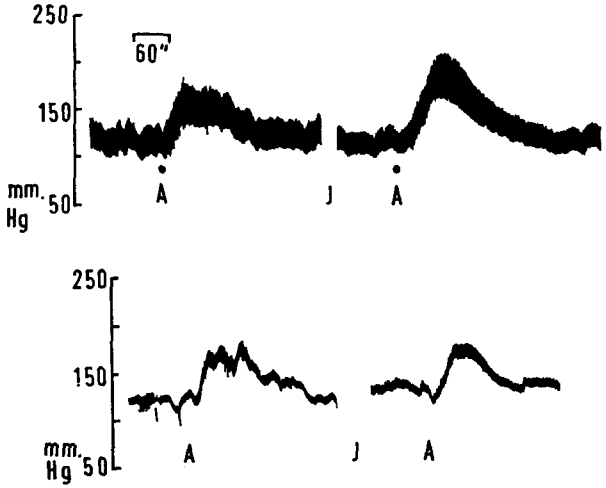

FIG. 2. Blood pressure record in a conscious dog. A = i.v. injection of adrenaline 1 μg./kg. J = i.v. injection of JB-329 0·5 mg./kg. The upper record shows the response to adrenaline before and after JB-329. The lower record, from the same dog, shows the response to adrenaline before and after JB-329, following treatment with *p*-phenylmandelic acid (5 mg./kg. i.v. daily for seven days). Potentiation of adrenaline pressor response by JB-329 does not occur after *p*-phenylmandelic acid.

Physostigmine salicylate, 0·04 mg./kg., in conscious dogs produced the same degree of peripheral antagonism as did THA and neostigmine. Dyflos, 0·3 mg./kg. produced the same peripheral antagonism.

JB-329 and p-phenylmandelic acid. In five conscious dogs given chronic medication with *p*-phenylmandelic acid (5 mg./kg. i.v. daily for seven days), JB-329 produced its usual effects: tachycardia, a rise in mean arterial pressure of 10–30 mm.Hg, and a decreased pulse pressure. However, the potentiation of the pressor responses to adrenaline and noradrenaline normally found after JB-329, 0·5 mg./kg. i.v., did not occur in four of the five dogs tested (Fig. 2). Despite this, the response to acetylcholine 0·5 μg./kg. was still abolished by JB-329 and the responses to other neurohumors were not significantly affected.

In single doses of 5 mg./kg. i.v., *p*-phenylmandelic acid in conscious dogs did not significantly alter any of the effects of JB-329. The same result was obtained in anaesthetised cats given 5–10 mg./kg. *p*-phenylmandelic acid.

Atropine and antagonists. THA produced antagonism to the peripheral effects of atropine similar to that against JB-329 described above.

Single doses of *p*-phenylmandelic acid, as with JB-329, produced no antagonistic effect to the peripheral actions of atropine.

Discussion

Atropine and JB-329 produce essentially the same peripheral pharmacological effects. In the same dose, both slightly raised blood pressure, reduced pulse pressure, induced marked tachycardia and produced the other autonomic changes expected of atropine-like compounds. The responses to the neurohumoral amines were modified in the same way.

Both compounds are stated to produce similar behavioural responses in unrestrained conscious dogs (Bell and others, 1963). JB-329 (0·5 mg./kg.) produced anti-acetylcholine effects on autonomic responses, followed by incoordination, ataxia, apparent disorientation and agitated behaviour. These authors reported that atropine 0·5 mg./kg. produced only autonomic changes, but that larger doses (1 mg./kg.) produced a syndrome identical to that of JB-329. In other behavioural studies with dogs (Goldenberg 1957; White and others, 1961) large doses of atropine (1·5 mg./kg.) produced similar results, although 0·5 mg./kg. did not induce bizarre behaviour. Edery (1962) stated that injection of 0·5 mg. atropine into the cerebral ventricles was without effect, but 1 mg. produced disturbed behaviour suggestive of the production of hallucinations. Horowitz and Chow (1962) concluded that JB-329 appeared to have a more potent central effect than atropine but about the same magnitude of peripheral side-effects. It appears that whilst the effects of atropine and JB-329 in animals are similar, the atropine effects on behaviour appear only with higher doses than are required with JB-329.

Various clinical reports of atropine poisonings (Alexander and others, 1946, Grossier 1956, Welbourn and Buxton 1948) describe the patients as suffering from disorientation, confusion, delirium, visual hallucinations and muscular incoordination. Many other synthetic atropine-like compounds produce similar behavioural alterations (Fink 1960, Pfeiffer and others, 1959).

The antagonism of the central effects of JB-329 by THA (Gershon, 1960; Gershon and Olariu, 1960; Bell and others, 1963) and the series of glycolic acid derivatives (Bell and others, 1963), is of interest because it may give insight into the mode of action of atropine-like compounds. In view of the atropine-like activity of JB-329 and the apparent involvement of acetylcholine in the syndrome, the anticholinesterase activity of THA seemed a logical basis for explaining the antagonism. We have shown that the anticholinesterases neostigmine, physostigmine and DFP parallel the peripheral antagonism of JB-329 shown by THA. However, neostigmine in man (Abood and others 1959), dyflos, physostigmine in rats

(Abood and others, 1959; Abood, 1959) and dogs (Bell and others, 1963) have proved ineffectual in antagonising the severity of the central disturbances produced by JB-329. Non-penetration originally seemed a possible explanation for the lack of antagonism, but there is much evidence that all these compounds exert an inhibitory action on the cholinesterase within the brain (Douskaya and Khaunina, 1961; Irwin and Hein, 1962).

THA is a monoamine oxidase inhibitor (Kaul, 1962), but another monoamine oxidase inhibitor, nialamide has been found to be ineffective in antagonising the behavioural changes produced by JB-329 in dogs (Bell, 1962). It is therefore difficult to see how the effects of THA can be attributed to its inhibition of cholinesterase or monoamine oxidase.

In view of the reported choline acetylase inhibition produced by THA (de la Lande, 1956) it is of interest that some members of the series of glycolic acid derivatives also inhibit choline acetylase (Garratini and others, 1958). Several of this latter series produce antagonism to the behavioural effects induced by JB-329 in dogs (Bell and others, 1963). It seems unlikely, however, that this action could be of importance, because JB-329 and atropine are very powerful acetylcholine antagonists.

The pharmacology of the members of the series of the glycolic acid derivatives studied here did not indicate any very strong cardiovascular or autonomic effects. The only obvious effects were potentiation of the depressor responses to acetylcholine and adrenaline by *p*-phenylmandelic acid, the 2- and 3-phenanthrylglycolic acids and phenoxymandelic acid. These compounds, with the exception of phenoxymandelic acid, were found by Bell and others (1963) to be active against behavioural changes induced by JB-329.

The responses to noradrenaline and adrenaline were shown to be markedly potentiated by JB-329. Chronic *p*-phenylmandelic acid medication in conscious dogs antagonised this adrenergic potentiation (Fig. 2). This effect was also produced by THA but also by the other anticholinesterases. It is interesting to note in this context that adrenaline blocking agents have been shown to antagonise the psychotomimetic action of lysergic acid diethylamide (Murphree, 1962; Elder and Dille, 1962).

It is apparent that the pharmacological basis for the action of the acetylcholine blocking psychotomimetic compounds and their antagonists is as yet not established. Abood (1961) pointed out the possibility that psychotropic agents may exert a direct action at central receptor sites and that the so-called neurohumoral amines merely define the chemical configuration of these receptor sites. Receptor site action by JB-329 was also favoured by Bell and others (1963) in explaining the action of the behavioural antagonists.

The findings in this study show that in addition to direct cholinergic effects, the antagonists inhibit the adrenergic responses potentiated by JB-329 and atropine. These effects should be considered in the light of Biel's proposal (1962) of a balance existing between sympathetic and para-sympathetic centres or functions in the central nervous system. However, the failure of all anticholinesterases to counteract central effects produced by these acetylcholine antagonising psychotomimetics

still cannot be explained. The hypothesis of Abood (1961) that psychotropic substances, in general, may exert a direct action at receptor sites deserves greater attention.

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