Biochemical Pharmacology, Vol. 34, No. 19, pp. 3591–3596, 1985.
Printed in Great Britain.

0006-2952/85 $3.00 + 0.00

PROPERTIES OF A Ca^{2+} AND Mg^{2+} STIMULATED ATPase IN THE RAT CAUDATE NUCLEUS

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(*Received* 3 *October* 1984; *accepted* 11 *March* 1985)

Abstract—Adenosine triphosphatase (ATPase) activity which could be stimulated maximally by either Ca^{2+} or Mg^{2+} was identified in a synaptosomal fraction from rat brain caudate nucleus. The thermodynamic properties of the Ca^{2+} and Mg^{2+} stimulated enzymes were similar to each other. Oligomycin, sodium azide and dinitrophenol had no significant inhibitory effects on stimulation by either cation. *In vitro* incubation of the ATPase with *cis*- or *trans*-flupenthixol, chlorpromazine or trifluoperazine, but not with haloperidol, significantly inhibited stimulation by either cation. The DA receptor agonist 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) inhibited stimulation of the enzyme by either cation, while *d*-amphetamine, SKF 38393, pergolide and LY-171555 had no significant effects. Nomifensine at 10^{-3} M inhibited the cation stimulation by about 33%. *In vivo* administration of dopamine (DA) receptor antagonists (haloperidol, *cis*-and *trans*-flupenthixol, spiperone, chlorpromazine and trifluoperazine) and the agonist apomorphine neither inhibited nor stimulated ATPase activity. It appears from these data that the ATPase activity is not under DA receptor modulation. In addition, our tentative conclusion is that one enzyme is involved, because both Ca^{2+} and Mg^{2+} produced similar maximal stimulations, the activities as a function of temperature were similar, the enzyme could not be further stimulated with Ca^{2+} after maximal stimulation by Mg^{2+} (and vice versa), and the behaviour of the ATPase activity to all drugs tested was similar.

Calcium plays an important role in neurotransmitter function in the central nervous system. During depolarisation, Ca^{2+} channels open and Ca^{2+} flows down an electrochemical gradient to the terminals. This elevation of intraterminal Ca^{2+} is believed to couple depolarisation with neurotransmitter release. Several mechanisms have been proposed for the removal of this elevated Ca^{2+} and at least some of these utilise adenosine triphosphatases (ATPases) [1–5]. In view of our interest in the pharmacology of drugs affecting dopamine (DA) neurotransmission, we have been examining the properties of ATPases in the DA-rich caudate nucleus. The function of this nucleus is relatively well defined, and the actions of drugs active on the DA system in this nucleus are well documented. The present paper describes the presence of Ca^{2+} and Mg^{2+} stimulated ATPase activity in a synaptosomal fraction from rat brain caudate nucleus. We investigated some basic properties of this ATPase activity and, because DA receptor agonists and antagonists affect neurotransmitter release [6] and might be predicted to influence enzymes involved in such release, we studied the ATPase sensitivity to *in vitro* and *in vivo* treatments with some drugs that affect DA neurotransmission.

MATERIALS AND METHODS

Tissue preparation. Adult male Sprague–Dawley rats were housed under a 12 hr light–dark cycle (dark 6:30 p.m. to 6:30 a.m.) at 22 ± 2° on a standard laboratory rat diet. After appropriate pretreatments, rats were stunned by a blow to the head, their brains were removed, and the caudate nuclei was excised into 0.32 M sucrose. A crude mitochondrial pellet was prepared by differential centrifugation, and a crude synaptosomal fraction (and in some cases an enriched mitochondrial fraction) was isolated by sucrose gradient centrifugation [7]. Tissue was routinely frozen in 0.32 M sucrose at −20° until use, 1–3 days later.

Analysis of ATPase activity. ATPase activity was determined [8] in tubes containing 25 mM Tris buffer (pH 7.4), 33 mM KCl, 0.1 mM EDTA, 1.0 mM ouabain, various concentrations of either Ca^{2+} or Mg^{2+} and various other chemicals as specified in the text. The reaction was started by the addition of ATP (1 mM final concentration). Samples were incubated at 37° for 30 min (the reaction was linear for at least 40 min) and terminated by the addition of 100 μl of 20% perchloric acid. Precipitated protein was removed by centrifugation, and phosphate (P_i) was measured spectrophotometrically according to Atkinson *et al.* [9]. Protein was determined by the method of Lowry *et al.* [10].

Chemicals. The names and sources are: 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene HBr (ADTN, Calbiochem, San Diego, CA, U.S.A.); pergolide mesylate and LY-171555 (Eli Lilly, Indianapolis, IN, U.S.A.); equine disodium ATP, ouabain, and oligomycin (Sigma, St. Louis, MO, U.S.A.); apomorphine HCl (Sigma, St. Louis, MO, U.S.A. and Sandoz†, Sydney, Australia); chlorpromazine HCl (May & Baker†, Sydney, Australia); nomifensine hydrogen maleate (Hoechst†, Frankfurt, West Germany); SKF38393, *d*-amphetamine sulfate, and trifluoperazine HCl (Smith, Kline & French†, Welwyn Garden City, England, and Sydney, Australia); *cis*- and *trans*-flupenthixol (Lundbeck†, Copenhagen, Denmark); spiperone (Janssen†,

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† Companies that donated drugs.

Beerse, Belgium); and haloperidol (Searle*, Sydney, Australia). All other chemicals were AR grade.

For *in vitro* studies, all drugs except ADTN, pergolide, haloperidol, oligomycin and apomorphine were dissolved in distilled water. ADTN and haloperidol were dissolved in a minimum of HCl and diluted to volume with Tris buffer (pH 7.4). Oligomycin was dissolved in absolute ethanol. Apomorphine was dissolved in 0.05% ascorbic acid. Pergolide was initially dissolved by gentle warming in dilute tartaric acid solution. Control incubations always included an appropriate vehicle, and the pH of all incubations was between 7.2 and 7.4.

For *in vivo* studies, all drugs except haloperidol, spiperone and apomorphine were dissolved in distilled water. Haloperidol and spiperone were dissolved in a minimum of glacial acetic acid and diluted to volume with distilled water. Apomorphine was dissolved in 0.05% ascorbic acid. All drugs were administered intraperitoneally (i.p.) in a dose-volume of 1 ml/kg, with an appropriate vehicle being administered to control animals. In these studies, control and drug-treated animals were always run in parallel from the time of injection to the completion of the ATPase assay.

Statistics. Enzyme kinetics were analysed using the method of Hanes [11]. In some cases standard linear regressions were calculated, and drug effects were assessed by analysis of variance followed by the Newman–Keul's procedure [12]. Only significant results of interest are presented.

RESULTS

Kinetic constants. Both Ca^{2+} and Mg^{2+} stimulated the hydrolysis of ATP with the optimal concentration of each ion being between 1 and 2 mM. The kinetic constants of hydrolysis were calculated using twelve concentrations of Ca^{2+} and eleven or twelve concentrations of Mg^{2+} (raw data not shown). For hydrolysis activated by Ca^{2+}, the $K_{m(apparent)}$ was 274 ± 31 μM (mean ± S.E.M. of N = 9 replicates) and the $V_{max(apparent)}$ was 215 ± 12 (N = 9) nmoles $P_i \cdot min^{-1} \cdot (mg\ protein)^{-1}$. For activity stimulated by Mg^{2+}, the $K_{m(apparent)}$ was 429 ± 44 μM (N = 7) and the $V_{max(apparent)}$ was 147 ± 14 nmoles $P_i \cdot min^{-1} \cdot (mg\ protein)^{-1}$ (N = 7).

In the presence of 1 mM Ca^{2+} or 1 mM Mg^{2+}, the enzyme was maximally stimulated by 500–1000 μM ATP with a $K_{m(apparent)}$ of 85 μM (75 and 95 μM, N = 2) and 92 ± 2 μM (N = 3) respectively (raw data not shown).

In a separate experiment, the combination of both cations in various concentrations (Table 1) did not produce any significant additional effect above that seen with either cation alone.

Effect of temperature. In the presence of 1 mM Ca^{2+}, the ATPase activity curve exhibited a discontinuity at 21.2°. Below and above this temperature the energies of activation were 8.9 and 4.3 kcal/mole (N = 3) respectively. In the presence of 1 mM Mg^{2+}, a discontinuity in the curve occurred at 23.5°, with the energies of activation below and above this point being 10.1 and 6.1 kcal/mole (N = 3) respectively. These results indicate that the enzyme activity behaved similarly to both cations.

Characterisation of the enzymes. Because a possible source of contamination of synaptosomal membranes is from disrupted mitochondria, we compared the sensitivity to inhibition by various drugs of ATPase from an enriched mitochondrial fraction with that from the synaptosomal fraction. The drugs were used in concentrations according to Ref. 13. To enable comparison between control and drug incubations, the data are expressed in Table 2 as percent inhibition, while the specific activities of control tubes are given in a table footnote. Sodium azide, dinitrophenol and oligomycin were without significant effect in the syaptosomal fraction (Table 2). Dinitrophenol was also inactive in the enriched mitochondrial fraction, while sodium azide produced significant inhibition in this fraction. Oligomycin, which inhibits mitochondrial Ca^{2+} uptake [14], was about five times more effective in inhibiting the activity in the mitochondrial than in the synaptosomal fraction (Table 2), indicating that about 50% of the mitochondrial, but only about 10% of the synaptosomal, activity was due to oligomycin-sensitive mitochondrial ATPase.

Effects of drugs in vitro. All drugs were tested at

* Company that donated drugs.

Table 1. Effect of combining various concentrations of Ca^{2+} and Mg^{2+} on ATPase activity in rat brain caudate nucleus*

	ATPase activity (nmoles $P_i \cdot min^{-1} \cdot mg^{-1}$)				
	Ca^{2+} concn (mM)				
Mg^{2+} concn	0	0.1	0.5	1.0	2.0
0	0 ± 1	27 ± 1	133 ± 4	144 ± 3	116 ± 17
0.1	28 ± 5	64 ± 9	135 ± 6	141 ± 6	129 ± 10
0.5	101 ± 11	112 ± 16	134 ± 12	131 ± 8	119 ± 10
1.0	137 ± 11	153 ± 16	133 ± 14	124 ± 10	110 ± 11
2.0	144 ± 14	149 ± 19	126 ± 15	121 ± 14	107 ± 13

* Data are expressed as the means of stimulated ATPase activity ± S.E.M. of three replicates, with the results being expressed relative to the activity present when neither cation was included.

Table 2. Effects of various chemicals on Ca^{2+} and Mg^{2+} stimulated ATPase activities in synaptosomal (syn) and enriched mitochondrial (mito) fractions from rat brain caudate nucleus*

Treatment	Fraction	% Inhibition	
		Ca^{2+}-ATPase	Mg^{2+}-ATPase
Control (no drug)	syn	0†	0†
	mito	0‡	0‡
Sodium azide, 100 μM	syn	9 ± 2 (4)	4 ± 1 (4)
	mito	36 ± 14§ (4)	49 ± 22§ (3)
Dinitrophenol, 100 μM	syn	1 ± 2 (4)	4 ± 1 (4)
	mito	7 ± 2 (3)	6 ± 4 (3)
Oligomycin, 2 μg/ml	syn	8 ± 3 (4)	11 ± 1 (4)
	mito	45 ± 5§ (4)	54 ± 13§ (4)

* A concentration of 1 mM Ca^{2+} or Mg^{2+} was used. The data are expressed as the mean percent inhibition, relative to the appropriate controls (no drug) ± S.E.M. of (N) replicates.

† The specific activities of control tissues were always between 159 and 170, and 137 and 145 nmoles $P_i \cdot min^{-1} \cdot (mg\ protein)^{-1}$ for the Ca^{2+} and Mg^{2+} stimulated enzymes respectively.

‡ The specific activities of control tissues were always between 51 and 57, and 64 and 67 nmoles $P_i \cdot min^{-1} \cdot (mg\ protein)^{-1}$ for the Ca^{2+} and Mg^{2+} stimulated enzymes respectively.

§ Significant inhibition, $P < 0.05$.

three concentrations (10, 100 and 1000 μM). In some cases, precipitation of the incubation medium occurred at the highest concentration, and no data were obtained (see Table 3).

Of the DA receptor blockers tested, the phenothiazines trifluoperazine and chlorpromazine, and the thioxanthene *cis*-flupenthixol (together with its less active isomer *trans*-flupenthixol), inhibited stimulation by either cation to an equal degree (Table 3). Haloperidol, a butyrophenone, was without significant effect even at 1 mM.

The DA D_1 receptor agonist SKF 38393, and the indirectly acting DA receptor agonist, *d*-amphetamine, were without significant effect. Of the three selective DA D_2 agonists tested, ADTN produced significant inhibition at all concentrations with the degree of inhibition being significantly ($P < 0.05$) greater with the Mg^{2+} stimulation than with the Ca^{2+} stimulated activity. Pergolide and LY-171555 were inactive. Nomifensine, a selective DA uptake inhibitor, was inactive at 100 μM but exerted significant inhibition of stimulation at 1 mM.

It is noteworthy that, when a particular drug was inhibitory, it was always inhibitory to stimulation by

Table 3. *In vitro* effects of various drugs on the stimulation by Ca^{2+} and Mg^{2+} of ATPase activity in a synaptosomal fraction from rat brain caudate nucleus*

Drug tested	% Inhibition					
	Ca^{2+}-ATPase			Mg^{2+}-ATPase		
	Drug concn (μM)			Drug concn (μM)		
	10	100	1000	10	100	1000
Nomifensine		10 ± 5 (3)	33 ± 2† (3)		5 ± 4 (3)	32 ± 4† (3)
cis-Flupenthixol	20 ± 4† (3)	82 ± 3† (3)	ppt	16 ± 3† (3)	76 ± 3† (3)	ppt
trans-Flupenthixol	30 ± 1† (3)	87 ± 2† (3)	ppt	30 ± 3† (3)	89 ± 2† (3)	ppt
Chlorpromazine	10 ± 2 (3)	53 ± 2† (3)	ppt	10 ± 2 (3)	62 ± 2† (3)	ppt
Trifluoperazine	11 ± 6 (6)	72 ± 2† (3)	ppt	15 ± 4 (6)	78 ± 1† (3)	ppt
Haloperidol		8 ± 1 (3)	12 ± 6 (3)		14 ± 4 (3)	15 ± 5 (3)
SKF 38393		6 ± 1 (3)	11 ± 1 (3)		7 ± 4 (3)	12 ± 3 (3)
ADTN	8 ± 3 (3)	14 ± 4 (3)	23 ± 2† (3)	18 ± 4† (3)	32 ± 4† (3)	40 ± 1† (3)
Pergolide	7 ± 2 (3)	0 ± 5 (3)	ppt	2 ± 5 (3)	−2 ± 4 (3)	ppt
LY-171555	−3, −7	2 ± 2 (3)	−2 ± 2 (3)	1 ± 1 (3)	3 ± 2 (3)	7 ± 1 (3)
d-Amphetamine	1 ± 2 (3)	4 ± 3 (3)	5 ± 3 (3)	4 ± 2 (3)	4 ± 2 (3)	12 ± 1 (3)

* A concentration of 1 mM Ca^{2+} or Mg^{2+} was used in each case, with the final drug concentration being between 10 μM and 1 mM. Data are expressed as the mean percent inhibition of the ion stimulated ATPase ± S.E.M. of (N) replicates. To reduce inter-assay variability, control and drug-containing tubes were run in parallel and the data are expressed relative to the control on that day. The control values were always between 141 and 183, and between 130 and 160 nmoles $P_i \cdot min^{-1} \cdot (mg\ protein)^{-1}$ for the Ca^{2+} and Mg^{2+} stimulated enzymes respectively. In some cases, the reaction mixture precipitated (ppt) at the 1 mM drug concentration.

† Significant inhibition, $P < 0.05$.

Table 4. Effect of haloperidol (1.0 mg/kg, i.p., 1-hr pretreatment) or vehicle on the kinetics of Ca^{2+}- and Mg^{2+}-ATPases in synaptosomal membranes from rat brain caudate nucleus*

	Ca^{2+}-ATPase		Mg^{2+}-ATPase	
	$K_{m(apparent)}$ (μM)	$V_{max(apparent)}$ [nmoles $P_i \cdot min^{-1} \cdot$ (mg protein)$^{-1}$]	$K_{m(apparent)}$ (μM)	$V_{max(apparent)}$ [nmoles $P_i \cdot min^{-1} \cdot$ (mg protein)$^{-1}$]
After haloperidol	215 ± 38 (8)	206 ± 13 (8)	382 ± 34 (8)	158 ± 18 (8)
After vehicle	274 ± 31 (9)	215 ± 12 (9)	429 ± 44 (7)	147 ± 15 (7)

* Twelve concentrations of either Ca^{2+} or Mg^{2+} varying from 0 to 2 mM were used to determine $K_{m(apparent)}$ and $V_{max(apparent)}$. The data are the means ± S.E.M. of (N) replicates.

either cation and the degree of inhibition was similar (Table 3), with the exception of ADTN. This general trend was also evident with sodium azide, dinitrophenol and oligomycin (Table 2).

Effects of drugs in vivo. Drugs were administered to rats either 1 hr (antagonists) or 30 min (apomorphine) prior to killing the animals. At these times, marked behavioural effects were evident in the drug-treated animals—that is, intense stereotypy after apomorphine and sedation ranging through to catalepsy with the active DA receptor blockers. In all the *in vivo* experiments, the striata of two rats were pooled.

Haloperidol (1.0 mg/kg) had no effect on the kinetics of either the Ca^{2+} or the Mg^{2+} stimulated ATPase activity (Table 4). In the second experiment, other drugs were administered at the doses listed in Table 5. Neither the antagonists nor apomorphine exerted any significant effects on the stimulation by 1 mM of either cation, although a slight depression of both activities was noted on chlorpromazine.

DISCUSSION

We have been able to stimulate ATPase activity in a synaptosomal fraction of rat brain caudate nucleus by either Ca^{2+} or Mg^{2+}. Either cation seemed sufficient to maximally stimulate the ATPase activity, in agreement with data from rat cerebral cortex [15], and mouse [13] and rat [8] whole brain. A Mg^{2+} stimulated ATPase has also been described in rat brain caudate nucleus [16, 17]. Unlike some other workers [3, 8, 15], we were unable to demonstrate a Ca^{2+} stimulated ATPase with a strict Mg^{2+} dependence and this may be due to our use of tissue which had been frozen [18] and which had not been washed extensively in chelator solutions [19].

The kinetics of the ATP hydrolysis were similar to those reported elsewhere [3, 8, 13, 15], with the enzyme being more sensitive to Ca^{2+} than Mg^{2+}. Maximal stimulation occurred at 1–2 mM for both ions. However the $V_{max(apparent)}$ was somewhat greater for Ca^{2+} than for Mg^{2+} stimulated activity. Con-

Table 5. Effects of various drugs administered i.p. on the activity of Ca^{2+} and Mg^{2+} stimulated ATPase activity*

Drug pretreatment and dose†		ATPase activity (nmoles $P_i \cdot min^{-1} \cdot mg^{-1}$)	
		Ca^{2+}	Mg^{2+}
Vehicle		171 (2)	174 (2)
cis-Flupenthixol	2	178 (2)	179 (2)
trans-Flupenthixol	2	177 (2)	186 (2)
Vehicle		170 (2)	173 (2)
Spiperone	1	171 (2)	175 (2)
Vehicle		172 ± 4 (5)	162 ± 6 (5)
Chlorpromazine	15	159 ± 10 (5)	142 ± 9 (5)
Vehicle		162 ± 3 (3)	137 ± 3 (3)
Trifluoperazine	5	162 ± 4 (3)	135 ± 7 (3)
Vehicle		199 ± 4 (3)	174 ± 2 (3)
Apomorphine	3	200 ± 3 (3)	175 ± 4 (3)

* A concentration of 1 mM Ca^{2+} or Mg^{2+} was used in each case. The data are expressed as the means of stimulated ATPase activity with S.E.M. if appropriate, of (N) replicates.

† One-hour pretreatment, except for apomorphine which was 30-min pretreatment; dose, mg/kg.

centrations of Ca^{2+}, Mg^{2+} or ATP which were above optimal inhibited activity.

In the present study, the thermodynamic properties of the Ca^{2+} and the Mg^{2+} stimulated activity were similar to each other as well as to that reported by Duncan [3] for a Mg^{2+} stimulated enzyme, supporting the suggestion that only one enzyme moiety is present.

Ca^{2+} and Mg^{2+} stimulated activities in the synaptosomal fraction were not inhibited significantly by sodium azide, dinitrophenol or oligomycin, in agreement with Lin and Way [13]. Oligomycin and sodium azide, but not dinitrophenol, inhibited enzyme activity in a mitochondrial fraction. These data suggest that only a small fraction of the synaptosomal ATPase activity was of mitochondrial origin and indicate that there are major differences between the ATPases in the two subcellular fractions.

In our drug studies, we used both *in vitro* and *in vivo* methods on the basis that DA receptor antagonists or agonists might have either a direct or indirect effect on the ATPase activity under study. In the *in vitro* study, *cis*- and *trans*-flupenthixol, trifluoperazine and chlorpromazine, in that order of potency, inhibited both the Ca^{2+} and the Mg^{2+} stimulated activities while haloperidol was inactive. This effect of the phenothiazines agrees in general with the literature [15, 20, 21], with one group, however, reporting that haloperidol inhibited Mg^{2+}-ATPase in rat brain cerebral cortex synaptosomes [20]. Our data clearly indicate that the inhibition is unrelated to DA receptor antagonism because the order of potency at the DA D_2 receptor is haloperidol = *cis*-flupenthixol > trifluoperazine > chlorpromazine > *trans*-flupenthixol [22]. It also seems unlikely that the inhibition is mediated via the inhibition of calmodulin [23] because calmodulin is ineffective in stimulating either Ca^{2+} or Mg^{2+} stimulated enzymes [15, 23]. The inhibitory effects of the phenothiazines could depend upon their local anaesthetic activity [24] which might enable them to inhibit ATPase activity in a manner similar to the potent anaesthetic tetracaine. In our hands, 10 mM tetracaine inhibited both Ca^{2+} and Mg^{2+} stimulated activities by about 50% (unpublished observations), implying also that the enzyme activity may be related to ATP-dependent Ca^{2+} uptake in synaptosomes [25]. The effects of a specific DA D_1 agonist (SKF 38393, inactive) and of DA D_2 agonists (pergolide, inactive; LY-171555, inactive; ADTN, active) of the DA releasing compound (*d*-amphetamine, inactive) and of the DA uptake inhibitor (nomifensine, active) confirmed that any inhibition observed was unrelated to a specific effect at DA receptors. The apparent selectivity of the Mg^{2+}-ATPase to inhibition by ADTN is interesting. This was the only drug tested that revealed such a selectivity. Although it might be argued that this result supports the concept that the Ca^{2+}- and Mg^{2+}-ATPases are two separate entities, it needs to be remembered that in all other ways the behaviour of the two activities was similar. The differential effect of ADTN might depend upon a different conformation of the enzyme in the presence of the two cations.

In vivo, neither the neuroleptics nor apomorphine exhibited a significant effect, even though the doses chosen produced marked behavioural signs of DA receptor blockade (sedation and catalepsy) or stimulation (stereotypy). A trend towards inhibition was seen with chlorpromazine, and it is interesting that McNulty *et al.* [16], using chlorpromazine (10 mg/kg, 1-hr pretreatment) reported a 50% inhibition of Mg^{2+}-ATPase in a synaptosomal fraction from rat brain striatum.

Trifluoperazine, chlorpromazine and *cis*- and *trans*-flupenthixol were potent inhibitors *in vitro* but not *in vivo*, and this difference may depend upon the relative concentrations obtainable after *in vitro* versus *in vivo* use. High *in vitro* concentrations of lipophilic DA receptor blockers [22] produce non-specific membrane disturbing actions, such as anaesthesia, and such effects may be responsible for the *in vitro* inhibitory activity of the phenothiazines observed in the present study. Another possibility worth considering is that the drugs administered *in vivo* were eluted out during the extensive washing required during the subcellular fraction preparation. This would seem unlikely, however, for the active DA receptor blockers because they bind with high affinity to tissue binding sites and are very lipophilic [22].

In reviewing the behaviour of the Ca^{2+} and Mg^{2+} stimulated activities, it seems that the tentative conclusion that only one enzyme is involved can be drawn. Thus, the levels of maximal stimulation achieved with both ions were similar, the activities as a function of temperature were similar, the enzyme could not be further stimulated with Mg^{2+} after maximal stimulation by Ca^{2+} (and vice versa), and the responses of the ATPase activity to all inhibitors and drugs tested (with the exception of ADTN) were very similar. Such a conclusion is consistent with earlier reports [26, 27], and with preliminary subcellular distribution studies that indicate a similar subcellular distribution for the Ca^{2+} and Mg^{2+} stimulated activities [28]. Final confirmation of this possibility will await further study.

In conclusion, the enzyme activities studied appear to be insensitive, in a receptor specific manner, to DA agonists and antagonists. The insensitivity to DA drugs may indicate that the enzyme is not associated specifically with DA systems and that the enzyme is not modulated by DA active drugs. Further studies are in progress to investigate these possibilities.

Acknowledgements—We gratefully acknowledge the financial support of the Australian Research Grants Commission. Owen Jenkins is thanked for his help in the brain dissections. We are very grateful to Dr. Phil Beart of the Austin Hospital, Heidelberg, Australia, for providing samples of pergolide, ADTN and LY-171555.

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