Involvement of Microsomal Na$^+$/K$^+$ ATPase Activity in the Mechanism of Action of Dopaminergic D$_2$ Receptors

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Abstract: Problem statement: Our previous research has shown that mitochondrial ATPase may have a role in the action of dopaminergic D$_2$ receptors. It is therefore, thought of interest to investigate the effect of bromocriptine, sulpiride or their combination on the mitochondrial and microsomal ouabain sensitive and ouabain insensitive Na$^+$/K$^+$-ATPase in the liver of rats. **Approach:** *In vivo* treatment was carried out to study the effects of bromocriptine mesylate 10 mg kg^{-1}, sulpiride 10 mg kg^{-1}; or bromocriptine mesylate 10 mg kg^{-1} + sulpiride 10 mg kg^{-1}, compared to a control group, in order to measure liver Na$^+$/K$^+$-ATPase activity. The drugs were injected intraperitoneally daily for 14 days. Mitochondrial and microsomal fractions were obtained by the methods of Schwartz. **Results:** Pretreatment of rats with both bromocriptine and sulpiride given simultaneously resulted in complete abolition of stimulation caused by bromocriptine and inhibition that resulted from sulpiride on mitochondrial as well as microsomal ATPase activities. **Conclusion:** This study indicated that the *in vivo* administration of dopaminergic agonist and antagonist drugs result in a significant alteration not only in the mitochondrial ATPase enzyme activity but also in the microsomal ATPase enzyme activity. Therefore, it is quite possible that ATPase of the tow fractions play important physiological as well as pathological roles in the mechanism of action of dopaminergic receptors.

Key words: Bromocriptine, sulpiride, Na$^+$/K$^+$-ATPase, dopaminergic receptors

INTRODUCTION

Bromocriptine (2-bromo-α-ergocriptine) is an ergot polypeptide derivative that combines with dopamine receptors in various tissues[1]. Dopamine-agonist drugs are the treatment of choice for most patients with hyperprolactinemia[2,3]. Bromocriptine has been the reference compound and effectively suppresses prolactin secretion, restores gonadal function and shrinks prolactinomas[4]. Sulpiride is an antipsychotic drug that acts as a selective blocking agent of pre- and post dopamine receptors[5]. Bromocriptine was reported to inhibit monoamine oxidase enzyme in the hypothalamus and liver of the rat[6]. Bromocriptine was found to increase cAMP in the striatum[7] but not in the hypothalamus[8]. Sulpiride, on the other hand, did not cause any changes in cAMP levels in the striatum of rat[9]. In addition, sulpiride did not inhibit cytochrome P450 activities in human liver microsomes[10]. Dopamine is an endogenous catecholamine that exerts its actions by occupancy of specific receptors. Based on pharmacological and biochemical studies, dopamine receptors were classified initially into two main groups: The dopamine receptor linked to stimulation of adenylyl cyclase (D$_1$)[11,12] and the dopamine receptor not linked to adenylyl cyclase or linked to its inhibition (D$_2$)[13-16].

Another D$_1$-like receptor has also been linked to stimulation of Phospholipase C (PLC) activity[17-21], whereas the D$_2$ receptor can be linked to inhibition or stimulation of PLC depending on the cell that expresses it[22].

Our previous study indicated the stimulatory activity of bromocriptine and inhibitory activity of sulpiride on mitochondrial Na$^+$/K$^+$-ATPase activity in the liver of rat[23]. It was suggested that mitochondrial Na$^+$/K$^+$-ATPase may have a role in the action of dopaminergic-D$_2$ receptors. Furthermore, it revealed that bromocriptine caused significant elevations in the cyclic AMP contents of the liver[24]. Indeed, it was found that dopamine D2 receptor activation by bromocriptine leads to stimulation of Na$^+$/K$^+$-ATPase activity via the cAMP pathway[25].

Many years ago (1963), Schwartz published the methodology for determination of Na$^+$/K$^+$-ATPase activities in "microsomal" fraction from rat liver[26]. Also, 1997 Nobel Prize winner Skou[27] reported that microsomal membrane fractions from crab nerve

contain an ATP-hydrolyzing activity stimulated by concentrations of sodium and potassium usually found in intracellular and extracellular fluids, respectively[28]. This requirement for both sodium and potassium ions remain the fundamental characteristic of Na^+/K^+-ATPase. Since, bromocriptine is largely metabolized by the liver; this is inferred from the absence of unchanged drug in urine and its high extraction by the liver[29]. Therefore, it is thought of interest to study the effects of bromocriptine, sulpiride or their combination on the mitochondrial and microsomal insensitive Na^+/K^+-ATPase in the liver of rats.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 170 g were selected in this study. The rats were housed in groups (three or four in standard polypropylene cage) and maintained under standard laboratory conditions at an ambient temperature of $23\pm2°C$, relative humidity $50\pm15\%$ and normal photo period (12 h dark/12 h light). Commercial pellet diet (manufactured by Grani soils and Flour mills Organization Feed Mill) and water were provided ad libitum. Animals were divided into 4 groups, (n = 7 each), as follows: group 1, received bromocriptine mesylate 10mg kg^{-1}, group 2, received sulpiride 10 mg kg^{-1}; group 3, received bromocriptine mesylate 10 mg kg^{-1} + sulpiride 10 mg kg^{-1} and group 4: (control group), received a saline solution. The drugs were injected intraperitoneally daily for 14 days. The last dose was injected 1 h before the sacrifice of the animals. The Atlases activities were assayed biochemically as the following:

The homogenization medium: To prepare tissue homogenates for determination of Na^+/K^+-ATPase activities, rats were stunned and decapitated; the thorax and abdomen were immediately opened. Liver tissues were removed from all rats at the end of the experiment; each tissue was quickly excised and washed in the physiological solution. Tissues were blotted dry on (Whatman) filter paper and weighed. Mitochondrial and microsomal fractions were obtained by the methods of Schwartz[26]. To each sample we added 5 mL of homogenization medium and the tissue was homogenized for 30-120 sec. (HY-Homogenizer, FRG). The homogenization medium consisted of 0.25 M sucrose, 4 mM EDT A, 30 mM histidine HCL and 20 mM Hepes buffer; pH 6.8. Just before homogenization, 0.2 % sodium deoxycholate was added to isolation medium. Two fractions were collected, one

at 10,000 rpm (MSE) for 30 min at $4°C$[26] which represented the mitochondrial fraction and anther fraction collected at 80,000 rpm (MSE) for 30 min[26]. Pellets were washed with the isolation medium, suspended in 0.25 M sucrose containing 1 mM EDTA and 30 mM histidine at pH 7.0 and then stored for 14 days at -5°C. Storage at -5°C was reported to cause destruction of the Mg2-stimulated enzyme, thereby revealing the stimulation due to Na^+/K^+, which stimulation can be inhibited by ouabain[26,30].

The incubation medium: Consisted o f 3 mM ATP, 3 mM MgCl₂ 100 mM NaCI, 20 mM KCI and 30 mM Tris (pH 7.0). Generally 0.1 mL of enzyme suspension was equilibrated for 15 min at 37°C, then added to the incubation medium and the incubation continued for 15 min. Ouabain in a concentration of 10 -4 M was included in one set of experiment. The reaction was stopped by the addition of 0.1 mL of cold 50% trichloroacetic acid and aliquots of 0.5 mL were assayed for inorganic phosphates by the method of Gomorri[31] using Metal as reducing agent. ATP was added in the form of Tris-ATP, prepared from disodium adenosine triphosphate (Sigma Chemical Co.), according to the procedure of Schwartz et al.[32].

Drugs and chemicals: Bromocriptine mesylate was obtained from Sandoz Pharmaceutical Co., sulpiride from Laboratories Etudes et Development Chimiques. Arpajon, France.

Statistical analysis: All the data were subjected to statistical analysis using Student's t-test for non-paired samples[33].

RESULTS

Liver Na^+/K^+-ATPase activity from rats pretreated with bromocriptine showed significantly ($p<0.01$) higher activity compared to controls. Ouabain caused a significant, ($p<0.01$), inhibition of the Na^+/K^+-ATPase activity of control rats. Bromocriptine pretreatment caused significant ($p<0.01$) increase in ouabain sensitive and ouabain insensitive mitochondrial liver Na^+/K^+-ATPase. On the other hand, sulpiride caused a significant inhibition in both ouabain sensitive and ouabain insensitive liver mitochondrial Na^+/K^+-ATPase activity (Fig. 1 and 3; Table 1 and 3). Pretreatment of rats with both bromocriptine and sulpiride abolished completely the effects of either bromocriptine or sulpiride alone on both ouabain sensitive and ouabain insensitive liver mitochondrial Na^+/K^+-ATPase activity (Fig. 1 and 3; Table 1 and 3). Bromocriptine also

caused a significant (p<0.01) increase of ouabain-sensitive and ouabain-insensitive liver microsomal Na^+/K^+-ATPase activity (Fig. 2 and 3; Table 2 and 3).

Table 1: Effect of bromocriptine mesylate (10 mg kg^{-1}; IP for 14 days), sulpiride (10 mg kg^{-1}; IP for 14 days) or their combinations on the ouabain sensitive and ouabain insensitive of mitochondrial Na^+/K^+-ATPase activities in the liver of rats (n = 7, error bars represent standard error)

Treatment	Mitochondrial Na^+/K^+-ATPase activities in the liver ATPase μ moles/100 mg tissue h^{-1}	
	Oubain insensitive	Oubain sensitive
Control	28.0±0.8	23±0.6
Bromocriptine	43.0*±1.0	34*±0.4
Sulpiride	20.0*±0.6	16*±0.3
Bromcriptine + sulpiride	29.0±0.7	22±0.6

Samples were run in duplicates, N (number of rats) = 7; For isolation and incubation medium, see text. Value is mean ± SEM; 1: Bromocriptine mesylate, l0 mg kg^{-1}, IP for 14 days; 2: Sulpiride 10 mg kg^{-1}, i.p. for 14 days; *: Significantly (p<0.01) different from control group

Table 2: Effect of bromocriptine mesylate (10 mg kg^{-1}; IP for 14 days), sulpiride (10 mg kg^{-1}; IP for 14 days) or their combinations on the ouabain sensitive and ouabain insensitive of microsomal Na^+/K^+-ATPase activities in the liver of rats (n = 7, error bars represent standard error)

Treatment	Microsomal Na^+/K^+-ATPase activities in the liver ATPase μ moles/100 mg tissue h^{-1}	
	Oubain insensitive	Oubain sensitive
Control	65.00±2.0	47±0.8
Bromocriptine	86.0*±3.0	77*±4.0
Sulpiride	45.0*±3.0	26*±1.0
Bromcriptine + Sulpiride	65.00±2.5	47±0.8

Samples were run in duplicates, N (number of rats) = 7; For isolation and incubation medium, see text. Value is mean ± SEM; 1: Bromocriptine mesylate, l0 mg kg^{-1}, IP for 14 days; 2: Sulpiride 10 mg kg^{-1}, i.p. for 14 days; *: Significantly (p<0.01) different from control group
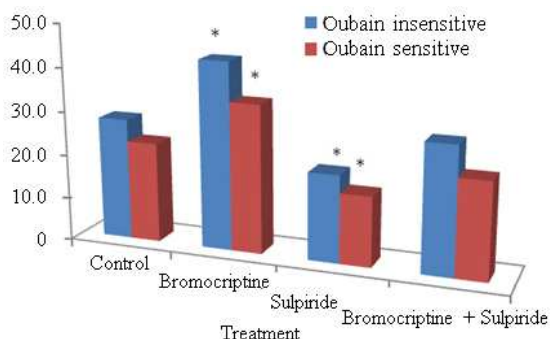

Fig. 1: Effect of bromocriptine mesylate (10 mg kg^{-1}; IP for 14 days) and sulpiride (10 mg kg^{-1}; IP for 14 days) on mitochondrial Adenosine-Triphosphatase (ATPase) activities of rat liver (n = 7, error bars represent standard error)

Meanwhile sulpiride caused a significant inhibition of microsomal ATPase activity of ouabain sensitive and ouabain insensitive Na^+/K^+-ATPase activity. Pretreatment of rats with both bromocriptine and sulpiride given simultaneously had resulted in complete abolition of both stimulation caused by bromocriptine and inhibition that resulted from sulpiride on microsomal ATPase activity (Fig. 2 and 3; Table 2 and 3).
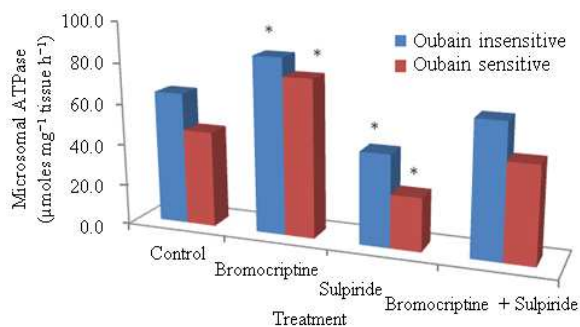

Fig. 2: Effect of bromocriptine mesylate (10 mg kg^{-1}; IP for 14 days) and sulpiride (10 mg kg^{-1}; IP for 14 days) on microsomal Adenosine-Triphosphatase (ATPase) activities of rat liver (n = 7, error bars represent standard error). Ouabin concentration = 10^{-4} M
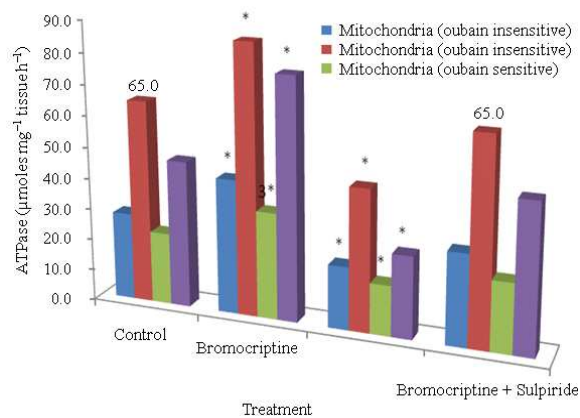

Fig. 3: Effect of bromocriptine mesylate (10 mg kg^{-1}; IP for 14 days) and sulpiride (10 mg kg^{-1}; IP for 14 days) on mitochondrial and microsomal Adenosine-Triphosphatase (ATPase) activities of rat liver (n = 7, error bars represent standard error)

Table 3: Effect of bromocriptine mesylate (10 mg kg^{-1}; IP for 14 days) and sulpiride (10 mg kg^{-1}; IP for 14 days) on mitochondrial and microsomal Adenosine-triphosphatase (ATPase) activities of rat liver (n = 7, error bars represent standard error)

Treatment	Microsomal ATPase μ moles/100 mg tissue h^{-1}		Mitochondrial ATPase μ moles/100 mg tissue h^{-1}	
	Oubain insensitive	Oubain sensitive	Oubain insensitive	Oubain sensitive
Control	65.00±2.0	47.00±0.8	28.00±0.8	23.00±0.6
Bromocriptine	86.0*±3.0	77.0*±4.0	43.0*±1.0	34.0*±0.4
Sulpiride	45.0*±3.0	26.0*±1.0	20.0*±0.6	16.0*±0.3
Bromcriptine + Sulpiride	65.00±2.5	47.00±0.8	29.00±0.7	22.00±0.6

Samples were run in duplicates, N (number of rats) = 7; for isolation and incubation medium, see text. Value is mean ± SEM; 1: Bromocriptine mesylate, l0 mg kg^{-1}, IP for 14 days; 2: Sulpiride 10 mg kg^{-1}, i.p. for 14 days; *: Significantly (p<0.01) different from control group

DISCUSSION

In this study ouabain (10^{-4}M) caused a significant, (p<0.01) inhibition of the Na$^+$/K$^+$-ATPase of control rats. Ouabain is a member of cardio-tonic steroids, which have been used clinically to treat congestive heart failure, this class of drugs that is widely used in clinical practice. In 1960, Skou showed that ouabain is an inhibitor of the Na$^+$/K$^+$-ATPase[34]. Results of the effect of bromocriptine pretreatment on both livers mitochondrial and microsomal showed a very clear stimulation of ATPase activities both in the presence and absence of ouabain. On the other hand, present research revealed that pretreatment of rats with sulpiride resulted into significant inhibition of the corresponding activities. The results in the mitochondrial and microsomal fractions were qualitatively similar. The experiments presented here demonstrate, for the first time, the comparison effect of dopaminergic agonist on ouabain sensitive and ouabain insensitive microsomal liver ATPase activities. These biochemical results, in addition to the detection of mitochondrial ATPase activity, also have been shown activity of microsomal ATPase, strongest correlations were found between the two isolated tested fractions. Also, results showed that bromocriptine and sulpiride were acting by both opposite and clearly antagonistic mechanisms in both fractions. These antagonistic mechanisms seemed to involve dopaminergic D$_2$ receptors since it was suppressed by the dopamine D$_2$ receptor antagonist, sulpiride[5]. It has been found that stimulation of D$_2$-like receptors leads to inhibition of Na$^+$-K$^+$-ATPase activity[11] and hyper-polarization; both effects are associated with the opening of K$^+$ channels[35]. Moreover, our previous study indicated the stimulatory activity of bromocriptine and inhibitory activity of sulpiride on mitochondrial Na$^+$/K$^+$-ATPase activity in the liver of rat[23] and it was suggested that mitochondrial Na$^+$/K$^+$-ATPase may have a role in the action of dopaminergic-D$_2$ receptors. The present results lend support to that suggestions since bromocriptine pretreatment on both liver fractions of

the mitochondrial and the microsomal ATPase have been showed a very clear stimulation of ATPase activities, these activities were clearly antagonistic by sulpiride. Indeed, Na$^+$/K+-ATPase is an important regulator of intracellular electrolyte levels in almost all mammalian cells[36,37]. The primary role of the Na$^+$, K$^+$-pump is therefore to maintain high intracellular K$^+$ and low intracellular Na$^+$. Failure of the Na$^+$, K$^+$-pump results in depletion of intracellular K$^+$, accumulation of intracellular Na$^+$ and, consequently, leads to membrane depolarization and increases in intracellular free Ca^{2+} due to activation of voltage-gated Ca^{2+} channels and a reversed operation of the Na$^+$/Ca^{2+} exchanger[38-40]. Since ATPase activities are well known to correlate with cation transport[36,37], the results would indicate that bromocriptine stimulates, where as sulpiride inhibits the transport of Na$^+$/K$^+$ in both fractions, therefore other cations such as Ca^{2+} may be affected[38-40]. Furthermore it has also been reported that the plasma membrane of many cell types contains a carrier which catalyzed the exchange of ions[41]. Stimulation of both liver mitochondrial and microsomal ATPase by bromocriptine, in contrast to inhibition of both liver mitochondrial and microsomal ATPase by sulpiride which may increase liver intercellular Ca^2 ions through an exchange Na^2/Ca^2 mechanism[41-48]. Furthermore, this result is in agreement with the findings that there is association between Ca^{2+} transport and the concentration of Na$^+$ and K$^+$, which has been demonstrated *in vitro*[49] and *in vivo*[50]. In addition, it has been suggested that dopamine D$_2$ receptor activation by bromocriptine leads to stimulation of Na$^+$/K$^+$-ATPase activity which may be mediated through inhibition of adenylyl cyclase in rat renal proximal tubules[25]. Indeed, it has been suggested that bromocriptine attenuates prolactin release by reducing Ca^{2+}[51]. Moreover it was suggested that the activity of Na$^+$/K$^+$-ATPase could modulate the production of Prostaglandins (PGs) in several tissues[52]. Also, Na$^+$/K$^+$-ATPase is the enzyme responsible for maintaining the low internal Na$^+$ and high internal K$^+$ concentrations typical of most vertebrate cells. The ion

gradients created by the enzyme are important in preserving the volume, pH and electrical resting potential of cells[53]. These results showed that bromocriptine and sulpiride were acting by both opposite and clearly antagonistic mechanisms, which is involved the action of dopaminergic D_2 receptors on the ionic transports at the levels of mitochondria and microsomal fractions.

CONCLUSION

This study indicated that the in vivo administration of dopaminergic agonist and antagonist drugs result in a significant alteration not only in the mitochondrial ATPase enzyme activity but also in the microsomal ATPase enzyme activity. Therefore, it is quite possible that ATPase of the tow fractions play important physiological as well as pathological roles in the mechanism of action of dopaminergic receptors.

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