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INFLUENCE OF BROMOCRIPTINE ON FREE AMINO ACIDS IN THE KIDNEYS AND HEART OF THE RAT

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Abstract—The effects of bromocriptine, sulpiride or their combination on free amino acids in the kidneys and the heart after acute and chronic treatment of rats were investigated, using an automatic LKB Amino Acid Analyzer. Bromocriptine at a single dose of 4 or 10 mg/kg (i.p.) did not affect the level of any amino acid; however, at a dose of 20 mg/kg it significantly elevated the content of taurine in the kidney from 7.00 ± 0.30 to 9.70 ± 0.1 and in the heart from 22.9 ± 1.7 to 30 ± 1.2 μmol/g wet tissue ($P < 0.05$, $N = 7$). It also increased glutamic acid in the heart from 3 ± 0.1 to 4.5 ± 0.25 μmol/g wet tissue ($P < 0.05$, $N = 7$). Chronic oral treatment of rats with bromocriptine (20 $mg \cdot kg^{-1} \cdot day^{-1}$) for 5 weeks significantly elevated the level of taurine in the kidney from 7.2 ± 0.3 (control) to 11.1 ± 0.90 and in the heart from 23.1 ± 1.7 to 38.8 ± 1.8 μmol/g wet tissue. It also increased cardiac glutamic acid content from 3 ± 0.1 to 4.8 ± 0.24 μmol/g wet tissue ($P < 0.01$, $N = 7$). Concurrent administration of sulpiride (20 mg/kg) significantly suppressed bromocriptine-induced increases in taurine and glutamic acid in both organs, suggesting an activation of D_2 receptors by bromocriptine. Due to the similarities between bromocriptine and the affected amino acids in renal and cardiac actions, it is suggested that mobilization of taurine and glutamic acid may at least in part contribute towards bromocriptine-induced renal and cardiac actions.

Bromocriptine (2-bromo-α-ergocriptine) has been shown to increase renal blood flow and to decrease renal vascular resistance and arterial blood pressure in some mammals [1, 2]. It has also been shown to protect guinea pigs against ouabain- and adrenaline-induced arrhythmias [3].

Studies on the cardiovascular actions of some free amino acids (AAs) showed that administration of taurine, glycine, glutamic acid or γ-aminobutyric acid into mammals decreases arterial blood pressure [4–6]. Furthermore, administration of aspartic acid or glutamic acid protects the myocardium and induced-recovery of cardiac function during experimentally induced myocardial ischemia [7, 8]. With regard to renal function, both glycine and glutamic acid have been shown to increase the glomerular filtration rate in dogs [9]. It was thus thought of interest to investigate the influence of bromocriptine administration on free AAs in the hearts and kidneys of rats.

MATERIALS AND METHODS

Male Sprague–Dawley rats (180–220 g) were divided into ten groups (N = seven rats/group). Each of the first six groups received one treatment of either saline (control), bromocriptine mesylate (4, 10 or 20 mg/kg), sulpiride (20 mg/kg) or bromocriptine (20 mg/kg) + sulpiride (20 mg/kg). All doses were injected i.p., and the animals were killed 2 hr later. Each of the other four groups was allowed to drink *ad lib.* water containing either no drug, bromocriptine, sulpiride or bromocriptine + sulpiride. The daily consumption of each of these drugs was adjusted to 20 mg/kg. Oral treatment continued for 5 weeks. After treatments, rats were stunned and decapitated, and the kidneys and hearts were removed. Each organ was washed in ice-cold Krebs' buffer and homogenized in ice-cold 6% aqueous perchloric acid (1 g tissue/6 ml acid). Homogenates were centrifuged at 10,000 rpm (MSE Centrifuge) for 20 min at 4°. The supernatant fractions were adjusted to pH 2.2 using aqueous 4 M KOH, allowed to stand for 1 hr at 0°, and centrifuged to remove the precipitated potassium perchlorate. The supernatant fractions were further centrifuged in an ultra centrifuge (Epperdorf Geratebau, 5414), and 20-μl aliquots were injected into the capsules and loaded on an LKB 4400 Amino Acid Analyzer (Biochrom Ltd., Cambridge, England). Free AAs were quantitated using standard AAs as detailed in the LKB manual. The concentration of each free AA was calculated as μmol per g wet tissue. Statistical significance of the results was calculated using Student's *t*-test for non-paired samples. Chemicals used were: bromocriptine mesylate (Sandoz), sulpiride (Laboratoire Etudes et Development Chimiques, Arpajon, France), ninhydrin (LKB), Li Pico buffers (Durrum Chemical Corp.) and amino acid standards (Benson Co.).

RESULTS

Acute studies. The principal free amino acids detected in the kidneys and heart of the rat are shown in Table 1. Acute treatment with bromocriptine

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Table 1. Normal free amino acid contents in rat kidney and heart

Amino acid	Free AA content (μmol/g wet tissue) Kidney	Heart
Tau	7.21 ± 0.30	23.10 ± 1.70
Asp	1.60 ± 0.10	0.57 ± 0.03
Thr	0.50 ± 0.06	0.22 ± 0.01
Ser	0.84 ± 0.05	0.29 ± 0.01
Glu	6.30 ± 0.30	2.97 ± 0.12
Gln	Not detected	3.88 ± 0.25
Gly	3.24 ± 0.15	0.51 ± 0.05
Ala	0.76 ± 0.05	1.33 ± 0.10

Values are means ± SEM, N = 7.

alone at either 4 or 10 mg/kg did not affect the content of any of the free amino acids in the kidney or the heart. However, at a dose of 20 mg/kg it significantly increased both taurine and glutamic acid in the heart and taurine in the kidney ($P < 0.05$, $N = 7$) (Table 2). Administration of sulpiride alone (20 mg/kg) did not affect the content of any amino acid but when co-administered with bromocriptine it significantly suppressed bromocriptine-induced increases in taurine and glutamic acid in both organs ($P < 0.01$, $N = 7$).

Chronic studies. Chronic oral treatment of rats with bromocriptine alone for 5 weeks significantly elevated free taurine and glutamic acid content in the heart and taurine in the kidney ($P < 0.01$, $N = 7$) (Table 2). There were slight increases in aspartic acid in both organs and of glutamic acid and glycine in the kidney. However, these increases were insignificant ($P > 0.05$, $N = 7$). Concurrent administration of sulpiride with bromocriptine blunted the increases observed in both glutamic acid and taurine in both organs ($P < 0.01$, $N = 7$) (Table 2).

DISCUSSION

Acute or chronic treatment of rats with bromocriptine (20 mg/kg) significantly elevated the content of free taurine and glutamic acid in the heart and of taurine in the kidney. These effects seemed to involve activation of dopamine D_2 receptors by bromocriptine since they were suppressed by the D_2 receptor antagonist, sulpiride [10]. The acutely induced increases may have resulted from selective increase in the transport of the affected amino acids from some organs to the heart and kidney. Such transport may result from activation of the enzyme γ-glutamyl transpeptidase present in these organs and implicated in amino acid transport across membranes [11]. The chronically induced changes may involve enhanced *de novo* synthesis and/or enhanced transport of the affected amino acids perhaps via stimulation of GH secretion. Indeed, bromocriptine stimulates GH release in normal mammals.

Bromocriptine-induced increase in renal taurine is of particular interest. Both taurine and bromocriptine are vasodilators [1, 2, 4, 12]. Bromocriptine-induced renal vasodilation and increase in renal blood flow are believed to involve direct activation of renal D_2 dopaminergic receptors on the vascular beds [13–15] and/or activation of presynaptic α_2-adrenoceptors or D_2 receptors on the sympathetic neurones with the ultimate decrease in release of the renal vasoconstrictor, norepinephrine [16–18]. In this connection it is interesting to note that taurine was observed to inhibit norepinephrine release from sympathetic nerve terminals [19] and to inhibit epinephrine release from the adrenal medulla [20]. It is thus tempting to suggest that the reported ability of bromocriptine to induce renal vasodilation and increase in renal blood flow [1] may involve, at least in part, mobilization of free renal taurine. In this

Table 2. Effects of acute and chronic treatments of rats with bromocriptine and sulpiride on free taurine and glutamic acid contents in the kidney and heart

Treatment	Taurine (μmol/g wet tissue) Kidney	Heart	Glutamic acid (μmol/g wet tissue) Heart
Acute*			
Control	7.0 ± 0.3	22.9 ± 1.7	3.0 ± 0.1
Bromocriptine			
4 mg/kg	8.3 ± 0.3	24.4 ± 2.0	3.0 ± 0.2
10 mg/kg	8.8 ± 0.2	27.0 ± 2.5	3.6 ± 0.3
20 mg/kg	9.7 ± 0.1†	30.0 ± 1.2†	4.5 ± 0.2†
Bromocriptine + sulpiride			
Each 20 mg/kg	7.5 ± 0.3	24.1 ± 1.5	3.3 ± 0.3
Chronic‡			
Control	7.2 ± 0.3	23.1 ± 1.7	3.0 ± 0.1
Bromocriptine			
20 mg/kg/day	11.1 ± 0.9§	38.8 ± 1.8§	4.8 ± 0.24§
Bromocriptine + sulpiride			
Each 20 mg/kg/day	7.4 ± 0.25	24.7 ± 1.5	3.1 ± 0.2

Values are means ± SEM, N = 7.

* Acute treatment: drugs were injected i.p. (single dose), and the animals were killed 2 hr later.

† $P < 0.05$, compared with control.

‡ Chronic treatment: drugs were administered *ad lib.* (20 mg/kg/day) for 5 weeks.

§ $P < 0.01$, compared with control.

regard, it is pertinent to recall that other sulfur-containing amino acids have been observed to improve kidney function in mammals [21].

Similarly, bromocriptine-induced increases in cardiac free taurine and glutamic acid may be of some importance. Both taurine and bromocriptine have been shown to exert antiarrhythmic activity in mammals [3, 22, 23]. In addition, taurine is a membrane stabilizer [24], and glutamic acid has been shown to improve cardiac performance and to protect the heart against cardiac ischemia [7, 8]. It is thus plausible to suggest that bromocriptine-induced increases in both glutamic acid and taurine may, at least in part, contribute to the observed cardiac protective action of bromocriptine in mammals [3, 23].

On a broad basis, it is possible to speculate on some potential applications of these results. First, bromocriptine-induced increase in renal taurine coupled with its ability to enhance arterial PGI_2 release [25] may prove of value in correcting renal blood flow insufficiencies. Second, bromocriptine-induced increases in cardiac glutamic acid and taurine may be beneficial in protecting the myocardium against insulting stimuli that precipitate ischemia and arrhythmias.

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