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Activation of Somatostatin Receptors in the Globus Pallidus Influences Rat Locomotor Activity and Increases cFos Expression in Brain Areas Implicated in Motor Control

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Key words: Basal ganglia, Somatostatin receptors sst_1, sst_2 and sst_4, locomotor activity, agonists and antagonists, c-Fos immunohistochemistry

INTRODUCTION

Somatostatin (SRIF) and its receptors ($sst_{1,2,4}$) have been localized in nuclei of the basal ganglia implicated in motor control, such as the striatum, the ventral pallidum and the globus pallidus. Their actual role in the basal ganglia has not yet been elucidated. The aim of the present study was to investigate a) the effect of SRIF and selective ligands, when infused in the globus pallidus (GP), on the locomotor activity of the rat and b) the resultant changes in neuronal activity in different brain regions.

METHODS

Male Sprague-Dawley rats, weighing 300-350 g, were used for all experiments. Guide cannulae were implanted bilaterally into the globus pallidus. A six days post-operative interval was allowed. SRIF (60,120,240 ng/0.5μl/side), L- 797,591 (sst_1 selective agonist 60, 120, 240 ng/0.5μl/side), L-779, 976 (sst_2 selective agonist, 120, 240, 480 ng/0.5μl/side), L-803,087 (sst_4 selective agonist 120,240 ng/0.5μl/side), SRA-880 (sst_1 selective antagonist + SRIF, 120 ng/0.5μl/side) and CYN154806 (sst_2 selective antagonist + SRIF, 120 ng/0.5μl/side) or saline were infused bilaterally in the GP of the rat and locomotor activity was measured for 60min using a rectangular activity cage. c-fos like immunoreactivity studies were performed to examine the somatostatin induced changes in neuronal activity. After the behavioral evaluation, rats were administered saline or somatostatin and 20 minutes later were decapitated. The brains were excised, frozen in isopentane at -40^{0}C and coronally sectioned at 12 μm using a cryotome. Sections were processed for For c-fos like immunoreactivity.

RESULTS

SRIF, infused in the GP, increased the locomotor activity of the rat in a statistical significant manner. This effect was mediated by the activation of the sst_1, sst_2 and sst_4 receptors, since their selective agonists increased locomotor activity in a dose dependent manner and the selective sst_1 and sst_2 antagonists reversed the somatostatin mediated locomotor activity to control levels. There are no sst_4 selective antagonists available to date. C-fos expression was increased in a statistically significant manner in the motor areas of the prefrontal cortex (209% as compared to control), the striatum (357% as compared to control) and the hippocampus (100% as compared to control).

CONCLUSIONS

This behavioral study provides functional evidence for the presence of sst_1, sst_2 and sst_4 receptors in the globus pallidus and supports the involvement of these receptors in motor control. In addition, cfos immunoreactivity provided evidence that brain regions involved in motor control are affected by somatostatin. Investigations are in progress in order to delineate the neurochemical routes via which the activation of somatostatin receptors in the globus pallidus mediates the enhancement of locomotor activity.

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Acute and Chronic Administration of Citalopram Influences Somatostatin Levels and Receptor Pharmacology in Brain

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Key words: Antidepressants, somatostatin receptor binding and autoradiography, peptide levels

PURPOSE

Antidepressants have been shown to influence somatostatin's function in selective nuclei of the basal ganglia. This study investigated the effect of acute and chronic administration of the antidepressant citalopram on somatostatin (SRIF) levels and somatostatin receptor subtype (sst_{1-5}) density in rat brain.

METHODS

The antidepressant treatment involved the ip administration of citalopram (20 mg/2ml/kg, once daily for 21 days; Chronic), saline and citalopram (2 ml/kg saline once daily for 20 days and 20 mg/2ml/kg citalopram once for one day; Acute), and saline (2 ml/kg once daily for 21 days; Control). Somatostatin levels were determined by radioimmunoassay. Somatostatin receptors were studied with [^{125}I]Tyr^{11} SRIF-14 binding in membrane preparations of prefrontal cortex (PFCx), nucleus accumbens (NAc), striatum and hippocampus. For the detailed mapping of somatostatin receptor changes within these brain areas, autoradiography studies were performed with [^{125}I]LTT SRIF-28 in the absence (labelling of sst_{1-5}) or presence of MK678 (3nM; labelling of $sst_{1/4}$) and [^{125}I]Tyr^3-octreotide (labelling of $sst_{2/5}$).

RESULTS

Acute and chronic administration of citalopram resulted in statistically significant increases of somatostatin levels in the PFCx (146±11% and 194±17%, respectively), Nac (180±19% and 156±15%, respectively) and striatum (161±20% and 151±22%, respectively). In the hippocampus, however, only chronically treated animals exhibited a significant increase of somatostatin levels (130±11%). [^{125}I]Tyr^{11} SRIF-14 binding in membranes obtained from the above mentioned brain areas was not affected by citalopram treatment. However, [^{125}I]LTT SRIF-28 binding with subsequent autoradiography in sections of brains of chronically treated animals significantly decreased in the superficial (s) and deep (d) layers of the frontal cortex (FrCx; frontal association, orbital and prelimbic cortex), and agra-nular insular cortex (Ais and Aid), while it increased in the CA1 field and all layers of the dentate gyrus. [^{125}I]LTT SRIF-28 binding in the presence of MK678 (3nM) and [^{125}I]Tyr^3-octreotide binding with subsequent autoradiography suggested that the sst_2 and $sst_{1/4}$ receptor subtypes are involved in the receptor changes observed in the FrCxd/Aid layers, and Aid layer/CA1 field, respectively.

CONCLUSIONS

These results suggest that citalopram administration affects somatostatin levels and the subsequent regulation of somatostatin receptor function in brain regions intimately involved in the emotional and motivational aspects of behavior.

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The Effect of Antihypertensive Treatment on Coagulation During Exercise

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Key words: Coagulation, nebivolol, quinapril, fibrinogen, von Willebrand factor

OBJECTIVE

Thrombotic events represent major complications of hypertension. Several thrombogenic abnormalities occur and essential hypertension is considered a pre-thrombotic condition. The aim of the study was to estimate the effect of acute stress on plasma coagulation, von Willebrand factor and fibrinogen in patients with essential hypertension and the effect of treatment with nebivolol vs quinapril.

DESIGN-METHODS

We studied 36 patients with essential hypertension (30 male, 6 female, 44.8±7.96 years old, BP 151.38±16.01/ 99.27±8.85mmHg). Treadmill exercise (modified Bruce protocol) was performed and prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen were determined. Patients were randomized to nebivolol 5mg (group N) or quinapril 20 mg (group Q) for a mean period of 5 months.

RESULTS

In group N, PT levels were 11.64±1.063 at baseline and decreased to 10.19±1.17 at exercise peak. After treatment PT levels were 11.62±0.99 and 10.94±0.96 respectively. In group Q, PT levels before treatment were 11.4±0.86 baseline and reduced to 10.91±087 at peak and after treatment 11.48±1.03 baseline, 10.88±0.95 at peak. PT level decrease during exercise before treatment was normalized after nebivolol treatment.

In group N, aPTT levels were 36.76±4.81 (baseline) and 30.64±4.42 (peak) and after treatment 36.83± 2.87, and 32.22±4.69 respectively. In group Q aPTT levels were 37.22±5.11 (baseline), 32.33±6.39 (peak) and after treatment 37.89±4.56 and 33.62±4.97.

In group N fibrinogen levels were 340.6±123.72 (before) and increased to 378.23±180.96 (peak) and after treatment were reduced to 333.61± 110.23 and 345.16±121.29 respectively. In group Q levels were 296.69±75.66 (baseline) and 310.64±95.98 (peak) and after treatment 301.31±80.38 and 330.8±117.81 respectively. Fibrinogen levels were decreased in group N and increased slightly but not significantly in group Q.

VWf levels in group N were 103.12±24.98 (baseline) and 94.75±30.57 (peak) and after treatment 100.13±26.34 and 113.37±46.61. In group Q levels were 104.7±28.37 (baseline) and 103.33±39.86 (peak) and 99±26.59, 102.7±33.81 after treatment.

CONCLUSIONS

During exercise plasma levels PT and aPTT decreased, von Willebrand factor levels slightly decreased and fibrinogen levels increased indicating a pre-thrombotic state. Nebivolol, a third generation b-blocker with vasodilatory properties ameliorated these changes equally to an ACE inhibitor quinapril. There was a trend for better results with nebivolol. The above results suggest that both drugs exert beneficial actions apart from blood pressure decrease.