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Short communication

Metabotropic glutamate receptor agonist (1*S*,3*R*-ACPD) increased frontal cortex dopamine release in aged but not in young rats

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Abstract

The effects of the metabotropic glutamate (mGlu) receptor agonist (1*S*,3*R*)-1-Amino cyclopentane-1,3-dicarboxylic acid (1*S*,3*R*-ACPD) infusion on frontal cortex dopamine extracellular levels were studied by microdialysis in young (3 months) and aged (24 months) rats. Basal dopamine levels were significantly higher in young than in aged rats. (1*S*,3*R*)-ACPD (1 mM) significantly increased dopamine efflux in aged rats, an effect which was antagonized by the mGlu receptor antagonist, (*S*)-α-methyl-4-carboxypheniylglycine (MCPG) (2 mM). On the contrary, (1*S*,3*R*)-ACPD up to the concentration of 2 mM failed to influence dopamine extracellular levels in young rats. These results suggest that the agonist of mGlu receptor group I and/or II can improve dopamine release under conditions of deficiency of extracellular dopamine concentration as observed in aging.

Keywords: Metabotropic glutamate receptor agonist; Dopamine; Cortex; Aging; Microdialysis

1. Introduction

The frontal cortex plays a significant role in the working memory, i.e., the brief retention and internalized information that controls behavior. This brain area has received great attention because its function is impaired in most patients with cognitive disorders (Goldman-Rakic, 1991, 1995; McCarthy et al., 1994). The glutamatergic and dopaminergic neurotransmitter systems are thought to be involved in age-related cognitive impairment (Palmer and Gershon, 1990) as well as in memory and learning disorders associated to neurological pathologies such as Alzheimer's disease (Fonnum et al., 1995) schizophrenia (Park and Holzman, 1992) and Parkinson's disease (Gotham et al., 1988; Levin et al., 1989). Several studies have demonstrated that increased glutamatergic activity leads to improvement of learning and memory retention (Flood et al., 1990). Glutamate receptor agonists such as cycloserine, a NMDA receptor partial agonist, and other compounds acting on ionotropic glutamate receptors may have a positive effect in patients with Alzheimer's disease (Sirvio et al., 1992; Fishkin et al., 1993), but their clinical use is limited by the multiple side-effects. The selective metabotropic glutamate (mGlu) receptor agonist, (1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*R*)-ACPD, has been shown to have two opposite effects, potentiation (Wang and Daw, 1996) or inhibition of glutamate-mediated excitotoxicity (Bruno et al., 1994). Moreover prefrontal cortex dopamine has been reported to play a significant role in the working memory (Goldman-Rakic, 1995) and an increased dopamine turnover in the prefrontal cortex has been correlated with impairment of spatial working memory performance in rats and monkeys (Murphy et al., 1996).

The influence of the glutamatergic on the dopaminergic system is well known (Cepeda et al., 1992). Some authors reported an effect of mGlu receptor agonist on dopamine release from the nucleus accumbens and the striatum (Sacaan et al., 1991, 1992; Ohno and Watanabe, 1995) in young rats. In the present microdialysis study, we examined both the direct effect of a metabotropic receptor agonist, (1*S*,3*R*-ACPD), active on both groups I and II of the mGlu receptor, on dopamine release in the frontal cortex, and the differences in response between young and aged rats.

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2. Materials and methods

Male Sprague–Dawley rats, aged 3 (200–250 g) and 24 months (700–800 g), were used. The animals were anesthetized with equitesin (pentobarbital sodium, 1% and chloral hydrate, 4.2%) and surgically implanted with a concentric dialysis probe (CMA12, 4 mm length) into the frontal cortex with a 40° incidence angle and the stereotaxic coordinates: A 1.7/2.2, L 0.5/0.7 (young/old rats), V 4.00 mm (atlas of Paxinos and Watson, 1986). Twenty-four hours later, the probe was perfused at a rate of 1.6 μl/min with Ringer's solution for at least 2 h until the dopamine levels stabilized. Samples were then collected into 5 μl 0.01 M $HClO_4$ every 30 min. The dopamine levels in the dialysates were measured 1 h before, during and up to 8 h after perfusion (1 h) of drugs. (1*S*,3*R*)-ACPD (0.6, 1 mM) and (*S*)-α-methyl-4-carboxypheniylglycine MCPG (2 mM) solutions were freshly prepared using Ringer's perfusion medium as vehicle. The dopamine content of all samples was measured by reverse-phase high performance liquid chromatography coupled to an electrochemical detector (ESA Coulochem II, Model 5200, Bedford, MA, USA). The results were expressed as mean ± S.E. ($n = 3$) dopamine dialysate concentrations, as percentages of basal values without probe recovery correction. At the end of each experiment the rats were killed with an overdose of equitesin and the brain was fixed with 4% paraformaldehyde. Coronal sections (40 μm thick) were made to verify the site of the probe.

3. Results

Basal dopamine levels, determined from the pooled data from animals before drug infusion, were significantly higher in young than in aged rats (7.38 ± 0.83 vs. 3.15 ± 0.15 pg/20 μl, $n = 12$, $P < 0.0001$ by Student's *t*-test). Aged rats had a marked increase in dopamine extracellular

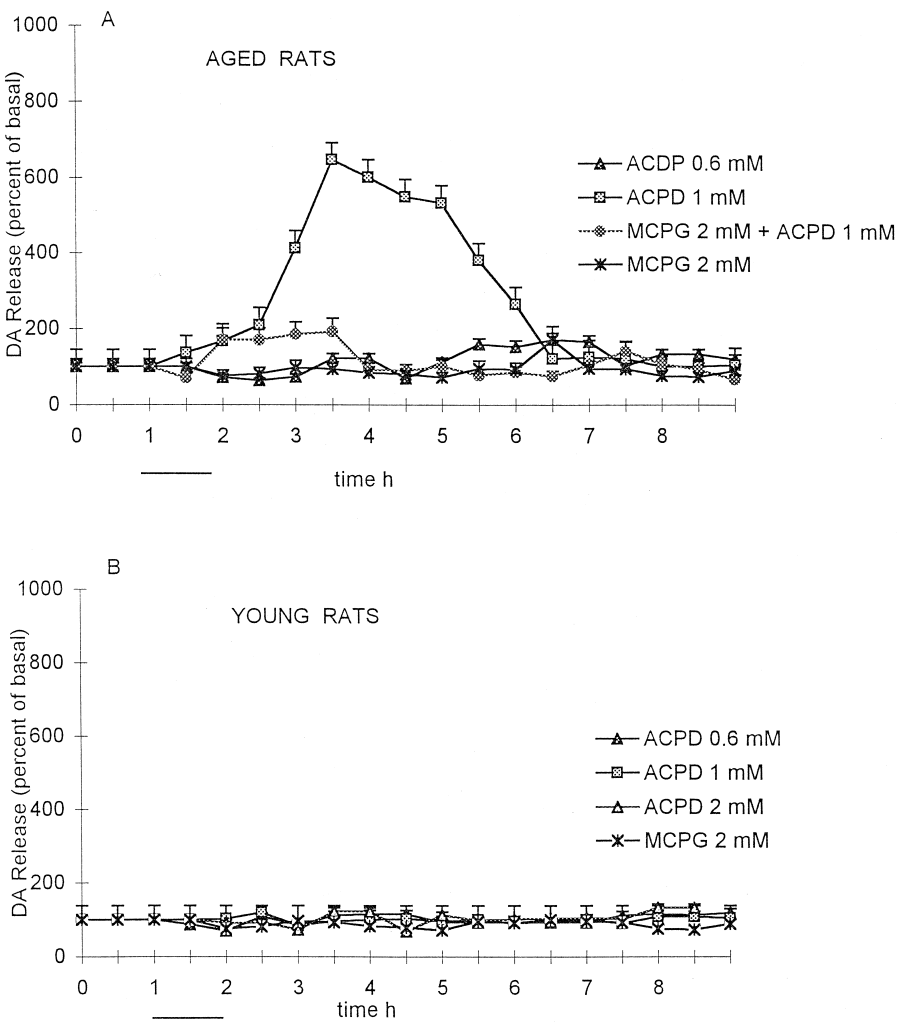

Fig. 1. Effects of local infusion of (1*S*,3*R*) ACPD or/and MCPG on dopamine efflux in the frontal cortex of aged (A) and young rats (B). Each agonist or antagonist was dissolved in Ringer's solution at concentrations shown in the legend and was infused via a probe for 60 min. To evaluate the antagonist effect, MCPG was infused for 60 min before agonist application. Results show mean ± S.E. ($n = 3$) dopamine dialysates concentrations, without probe recovery correction, expressed as percentages of basal values.

levels after perfusion of 1 mM (1*S*,3*R*)-ACPD in the frontal cortex. This effect peaked 1.5 h after the end of agonist application, disappeared 2 h later and was completely antagonized by pretreatment with 2 mM MCPG (Fig. 1A). On the contrary, concentrations up to 2 mM of (1S,3R)-ACPD, had no significant effect on the extracellular dopamine levels of young rats (Fig. 1B). Moreover, infusion of the antagonist, MCPG, alone (2 mM) in both aged and young rats did not affect dopamine efflux (Fig. 1A and B). No noticeable behavioral effects were observed in either age group following drug infusion.

4. Discussion

The results showed that the extracellular levels of dopamine in the frontal cortex are significantly less (about 42%) in aged than in young rats. There are few data on the age-related modifications of dopamine levels. Conflicting results have been reported for the cerebral cortex, depending on the area and the methodologies used. Several studies of the steady-state levels of dopamine showed an age-related increase in the somatomotor and prefrontal cortex and a decrease in the temporal cortex, while others have reported a reduction of dopamine release from cortical synaptosomes (Carfagna et al., 1985; Godefroy et al., 1991). The impaired presynaptic function in the cerebral cortex seen with aging was thought to be due to a decrease in Ca^{2+} influx (Tanka et al., 1996; Hartmann et al., 1996). The present microdialysis study showed that the mGlu receptor agonist, (1*S*,3*R*)-ACPD, exerts a significant facilitatory effect on dopamine release in frontal cortex of aged but not of young rats. The increase in dopamine levels observed in aged rats peaked 90 min after perfusion. While at present we have no obvious explanations for the long latency of this effect of (1*S*,3*R*)-ACPD, the finding is consistent with the report of Sacaan et al. (1992) showing that unilateral intrastriatal injection of (1*S*,3*R*)-ACPD induces contralateral turning behavior at 1 h, reaching a plateau 3–6 h after injection. Furthermore, in methamphetamine-sensitized rats, the increase in dopamine release induced by intrastriatal (1*S*,3*R*)-ACPD has been reported to peak 1 h after the end of perfusion (Arai et al., 1996). At the dose of 0.6 mM (1*S*,3*R*)-ACPD, a small non-significant reduction in dopamine release was observed in aged rats (Fig. 1A). This finding is in line with the report of Taber and Fibiger (1995) showing opposite effects of different doses of (1*S*,3*R*)-ACPD on nucleus accumbens dopamine release. Our finding of increased effectiveness of (1*S*,3*R*)-ACPD in aged rats is consistent with results of in vitro studies showing a greater increase in dopamine release evoked by high K^+ in synaptosomes from frontal cortex and caudate in old than in young rats (Cerrito et al., 1993). The age-related difference in (1*S*,3*R*)-ACPD agonist mGlu receptor responsiveness suggests modifications in presynaptic G protein-mediated intracellular mechanisms. A region-specific down-regulation of free intracellular Ca^{2+} that occurs in the cortex of aged rats (Hartmann et al., 1996), and the greater susceptibility of aged rats to changes in calcium homeostasis could explain these results. The mGlu receptor agonist might also enhance glutamate release via protein kinase C more in aged than in young rats and therefore activate NMDA receptors, leading to an increase in dopamine levels. Aged-related changes in the expression and coupling of mGlu receptor subtypes to the phospholipase C signal transduction pathway can be hypothesized (Casabona et al., 1997).

The finding that perfusion with the antagonist, MCPG, did not itself produce a significant change in extracellular dopamine levels suggests the absence of tonic inhibition by metabotropic glutamate receptors in the regulation of dopaminergic neurotransmission in frontal cortex.

Since (1*S*,3*R*)-ACPD acts on groups I and II of mGlu receptor, further studies are necessary to determine which subtypes of mGlu receptor and intracellular mechanisms mediate dopamine release from the frontal cortex of aged rats, and to clarify their role in the neurodegeneration and impairment of learning and memory frequently encountered in aging individuals.

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References

Arai, I., Shimazoe, T., Shibata, S., Inue, H., Yoshmatsu, A., Watanabe, S., 1996. Enhancement of dopamine release from the striatum through metabotropic glutamate receptor activation in methamphetamine sensitized rats. Brain Res. 729, 277–280.

Bruno, V., Copani, A., Battaglia, G., Raffaele, R., Shinozaki, H., Nicoletti, F., 1994. Protective effect of metabotropic glutamate receptor agonist, DCG-IV, against excitotoxic cell death. Eur. J. Pharmacol. 256, 109–112.

Carfagna, N., Trunzo, F., Moretti, A., 1985. Brain catecholamine and turnover in aging rats. Exp. Gerontol. 20, 265–269.

Casabona, G., Knopfel, T., Kuhn, R., Gasparini, F., Baumann, P., Sortino, M.A., Copani, A., Nicoletti, F., 1997. Expression and coupling to polyphosphoinositide hydrolysis of group I metabotropic glutamate receptors in early postnatal and adult rat brain. Eur. J. Neurosci. 9, 12–17.

Cepeda, C., Radisavljevic, Z., Peacock, W., Levine, M.S., Buchwald, N.A., 1992. Differential modulation by dopamine of responses evoked by excitatory amino acids in human cortex. Synapse 11, 330–341.

Cerrito, F., Aloisi, G., Arminio, P., 1993. Age-related changes in rat brain monoamines release: peculiarity of dopamine release. J. Neurosci. Res. 34, 364–370.

Fishkin, R.J., Ince, E.S., Carlezon Jr., W.A., Dunn, R.W., 1993. D-Cycloserine attenuates scopolamine-induced learning and memory deficits in rats. Behav. Neural Biol. 59, 150–157.

Flood, J.F., Baker, M.L., Davis, J.L., 1990. Modulation of memory

processing by glutamic acid receptor agonists and antagonists. Brain Res. 521, 197–202.

Fonnum, F., Myhrer, T., Paulsen, R.E., Wangen, K., Oksengard, A.R., 1995. Role of glutamate and glutamate receptors in memory function and Alzheimer's disease. Ann. N.Y. Acad. Sci. 757, 475–486.

Godefroy, F., Bassant, M.H., Lamour, Y., Weil-Fugazza, J., 1991. Effect of aging on dopamine metabolism in the rat cerebral cortex: a regional analysis. J. Neural Transm. 83, 13–24.

Goldman-Rakic, P.S., 1991. Prefrontal cortical dysfunction in schizophrenia: the relevance of working memory. In: Caroll, B.J., Barrett, J.E. (Eds.), Psychopathology and the Brain. Raven Press, New York, NY, pp. 1–23.

Goldman-Rakic, P.S., 1995. Cellular basis of working memory. Neuron 14, 477–485.

Gotham, A.M., Brown, R.G., Marsden, C.P., 1988. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 111, 299–321.

Hartmann, H., Velbinger, K., Eckert, A., Muller, W.E., 1996. Region-specific downregulation of free intracellular calcium in the aged rat brain. Neurobiol. Aging 17, 557–563.

Levin, B.E., Labre, M.M., Weiner, W.J., 1989. Cognitive impairments associated with early Parkinson's disease. Neurology 39, 557–561.

McCarthy, G., Blamire, A.M., Puce, A., Nobre, A.C., Bloch, G., Hyder, F., Goldman-Rakic, P.S., Shulman, R.G., 1994. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. Proc. Natl. Acad. Sci. USA 91, 8690–8694.

Murphy, B.L., Arnsten, A.F.T., Goldman-Rakic, P.S., Roth, R.H., 1996. Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. Proc. Natl. Acad. Sci. USA 93, 1325–1329.

Ohno, M., Watanabe, S., 1995. Persistent increase in dopamine release following activation of metabotropic glutamate receptors in the rat nucleus accumbens. Neurosci. Lett. 200, 113–116.

Palmer, A.M., Gershon, S., 1990. Is the neuronal basis of Alzheimer's disease cholinergic of glutamatergic?. FASEB J. 4, 2745–2752.

Park, S., Holzman, P.S., 1992. Schizophrenics show spatial working memory deficits. Arch. Gen. Psychiatry 49, 975–982.

Paxinos, G., Watson, C., 1986. The Rat Brain Stereotaxic Coordinates. Academic Press, New York, NY.

Sacaan, A.I., Monn, J.A., Schoepp, D.D., 1991. Intrasriatal injection of a selective metabotropic excitatory amino acid agonist induces contralateral turning in the rat. J. Pharmacol. Exp. Ther. 259, 1366–1370.

Sacaan, A.I., Bymaster, F.P., Schoepp, D.D., 1992. Metabotropic glutamate receptor activation produces extrapyramidal motor system activation that is mediated by striatal dopamine. J. Neurochem. 59, 245–251.

Sirvio, J., Ekonsalo, T., Riekkinen Jr., P. Lahtinen, H., Riekkinen, P. Sr., 1992. D-Cycloserine, a modulator of the *N*-methyl-D-aspartate receptor, improves spatial learning in rats treated with muscarinic antagonists. Neurosci. Lett. 146, 215–218.

Taber, M.T., Fibiger, H.C., 1995. Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: modulation by metabotropic glutamate receptors. J. Neurosci. 5, 3896–3904.

Tanka, Y., Hasegava, A., Ando, S., 1996. Impaired synaptic functions with aging as characterized by decreased calcium influx and acetylcholine release. J. Neurosci. Res. 43, 63–76.

Wang, X.F., Daw, N.W., 1996. Metabotropic glutamate receptors potentiate responses to NMDA and AMPA from layer V cells in rat virtual cortex. J. Neurophysiol. 76, 808–815.