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Dopaminergic drugs may counteract behavioral and biochemical changes induced by models of brain injury

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Glutathione redox index

Abstract The dopaminergic drugs, bromocriptine, cabergoline, dihydroergocryptine, pergolide and ropinirole were injected subcutaneously (s.c.) at the dose of 0.1, 0.5 and 1 mg/kg/day for 7 days into male rats of the Sprague—Dawley strain. The drug pre-treatment reverted amnesia induced in rats by hypobaric hypopxia and tested in active and passive avoidance tasks. A restoration of memory retention, as assessed in a step-through passive avoidance task, was found in animals with a 2-month brain occlusive ischemia and exposed to dopaminergic drugs for 7 days. For behavioral effects in both active and passive avoidance tests in both experimental models, the rank of relative potency was ropirinole > bromocriptine = cabergoline > pergolide > dihydroergocryptine. Spontaneous ambulation of animals with brain occlusive ischemia was increased by the higher doses of drugs. All dopaminergic drugs reduced kainate mortality rate. The rank of relative potency for this effect was ropirinole = bromocriptine = cabergoline > pergolide = dihydroergocryptine. However, no change was found in other seizure parameters (latency to first convulsion and total number of convulsions) after drug treatment. A biochemical analysis of glutathione redox index (glutathione reduced/glutathione oxidized ratio) in discrete brain areas revealed that exposure to dopaminergic drugs increased this parameter in frontal cortex, striatum and hippocampus of animals subject to hypobaric hypoxia and brain occlusive ischemia. For this effect, the relative potency rank was ropirinole > bromocriptine = cabergoline >> pergolide = dihydroergocryptine. These behavioral and biochemical findings suggest that dopaminergic drugs may counteract either behavioral or biochemical changes induced by experimental models of brain injury. This activity was found after protective activity (as found in animals pre-treated with these drugs and exposed to hypobaric hypoxia) or reversal of brain injury (as found in animals treated after 2-month occlusive brain

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ischemia). Their neuroprotective activity probably involves the reduction/oxidation balance of the glutathione system in the brain.

1. Introduction

The clinical use of dopaminergic drugs is probably parallel to the history of modern neuropsychiatry. Today, these drugs are used in various pathological situations but primarily in Parkinson's disease (PD) and motor disturbances induced by L-DOPA (Calne et al., 1976; Martignoni et al., 1991; Rascol et al., 1996). Although dopaminergic drugs possess different profile of action, those used in clinical practice are mostly active as agonists of dopamine receptors. In particular, ergoline and non-ergoline dopamine D2 receptor agonists are used for the therapy of the above mentioned neurological disturbances. For instance, 1[6-allylergoline-8β-γl)carbonil]-1-[(3-dimethylamine)-propyl]-3-ethylurea (cabergoline) is an ergot alkaloid derivative that possesses dopaminergic activity both in vitro and in vivo. Together with the interaction with D2 dopamine receptors (Fariello, 1998), a metabolic mechanism of action has been postulated for cabergoline. This drug, in fact, has been found to exert antioxidant activity as it reduces lipid peroxidation in different rat brain areas (Finotti et al., 2000) and prevents necrotic neuronal death in a model of oxidative stress (Lombardi et al., 2002). Dihydroergocryptine is a dihydrogenated ergot alkaloid that interacts with dopamine D2 receptors located in the anterior pituitary (Sibley and Creese, 1983), in the striatum and nucleus accumbens (Marshall and Berrios, 1979). This drug also possesses antioxidant properties as it reduces glutathione/oxidized glutathione ratio (glutathione redox index) in the brain of aged rats (Benzi et al., 1988a). This effect has been related to the fact that dihydroergocryptine may affect some cerebral anti-oxidative enzyme activities in certain brain areas. Ropinirole (4-[2-(dipropylamino)ethyl]-2-indolinone monohydrochloridre) is a non-ergoline dopamine receptor agonist with high affinity for dopamine D2-like receptors in human caudate tissue and no activity on D1 dopamine receptors (Eden et al., 1991). Like cabergoline, ropirinole also improves the reduction/oxidation balance of the glutathione system in different brain areas and restores motor activity in models of brain injury (Medico et al., 2002). Thus, the concept that antioxidant activity is peculiar for dopaminergic drugs and plays a role in their therapeutic effects in neurodegenerative diseases seems to be substantiated (Gassen and Youdim, 1999).

Indeed, neuroprotection against oxidative stress may be an important factor in the treatment of PD, since free radical-induced damage is believed to play a major role in nigrostriatal dopaminergic neurodegeneration (Lipton and Rosenberg, 1994). Recently, dopamine D2 receptor agonists (i.e., bromocriptine, pergolide, ropinirole, pramipexole and cabergoline) have been introduced into clinical practice for improving symptoms and preventing the development of L-DOPA-induced neurotoxic effect (Jankovic, 2001). Excessive activation of cerebral dopamine metabolism by high-dose L-DOPA therapy may promote oxidative stress and thereby accelerate the rate of cell degeneration in the substantia nigra of patients with PD (Spina and Cohen, 1989; Ogawa et al., 1993a; Spencer Smith et al., 1994).

The present study was undertaken to examine the effects of dopaminergic drugs (bromocriptine, cabergoline, dihydroergocryptine, pergolide and ropinirole), administered a dose range of 0.1—1 mg/kg, on behavioral deficits induced in rats by models of brain injury of various type. The rationale for this study was based on the hypothesis that dopaminergic drugs may exert antioxidant activity explaining their protective action in models of brain injury. We were therefore interested in studying the effects of these drugs on brain glutathione redox system parallel with their behavioral effects in models of brain injury. As a result of these studies, a rank of relative potency of these drugs in behavioral and biochemical tests has been proposed. The demonstration of an improvement of the behavioral and biochemical changes induced by different types of brain damage may be useful for widening the clinical applications of dopaminergic drugs.

2. Experimental procedures

2.1. Animals

Male rats of the Sprague—Dawley strain (purchased from Charles River, Italy), weighing 280 ± 20 g were used throughout all experiments. The animals were housed two—three in plexiglas cages under a constant light—dark cycle (lights on between 8.00 and 20.00) at 21 °C. Commercial food and tap water were available ad libitum. All animals were used only once in the behavioral experiments. Experiments were carried out according to the European Community Council Directive 86/609/EEC and efforts were made to minimize animal suffering and to reduce the number of animals used.

Rats of the Wistar strain were selected for these experiments as they were chosen in previous studies with the same model (Medico et al., 2002). They did not appear to be unfavorable in ischemic models.

2.2. Surgery

For experiments on brain occlusive ischemia, a number of animals was subject to a manipulation of the four major arteries of the brain with a method similar to that described by Pulsinelli et al. (1982). Both vertebral arteries were cauterized after intraperitoneal (i.p.) injection of sodium pentobarbital (50 mg/kg) as anesthestetic and polyethylene cuffs PE-10 were placed loosely around the common carotid arteries without completely interrupting carotid blood flow. Two months after operation, all surviving animals showing no neurological gross abnormalities were admitted to drug treatment. Only 5 over 60 animals died after operation. Animals undergoing a sham operation were considered as controls.