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Research report

Brain sites mediating cyclosomatostatin-induced catalepsy in Wistar rats: A specific role for the nigrostriatal system and locus coeruleus

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ABSTRACT

A decrease in somatostatin activity is observed in the Parkinsonian brain. In recent experiments on rats, we simulated this abnormality by intracerebroventricular injections of a somatostatin antagonist, cyclosomatostatin. The treated animals displayed catalepsy, a state that resembles the extrapyramidal signs of Parkinson's disease. The neuroanatomical substrates mediating the catalepsy-inducing effect of cyclosomatostatin are unknown. To clarify this issue, we assessed here the action of cyclosomatostatin injected into the substantia nigra pars compacta (SNc), dorsal striatum (DS), locus coeruleus (LC), pedunculopontine tegmental nucleus (PPTg), and inferior colliculus (IC). The experiments were conducted with male Wistar rats of 270–290 g bw, catalepsy was evaluated by using the bar test. The injections into the PPTg and IC were without effect whereas the intra-SNc, intra-DS, and intra-LC administrations produced distinct cataleptic response. Thus, it was shown for the first time that the LC is a brain center capable of causing catalepsy. These data provide new insights into the neuroanatomical organization of the catalepsy-initiating mechanism and suggest the LC representing a potential target for therapeutic manipulations of extrapyramidal dysfunctions.

1. Introduction

Bradykinesia and other extrapyramidal dysfunctions are the major symptoms of Parkinson's disease (PD) (Hornykiewicz, 1998; Thomas and Beal, 2007; Magrinelli et al., 2016). Histopathologically, PD is characterized by neuronal injury across the brain, most prominently in the substantia nigra pars compacta (SNc), dorsal striatum (DS), and locus coeruleus (LC) (Kordower et al., 2013; review Ionov, 2008).

The development of extrapyramidal motor dysfunctions in PD is commonly attributed to central dopaminergic deficiency caused by the degeneration of SNc dopaminergic neurons and their axons in the DS; the degeneration of noradrenergic neurons in the LC presumably can aggravate the damage to nigral dopaminergic neurons (for Refs., see Hornykiewicz, 1998; Ionov, 2008). The precise molecular mechanism underlying parkinsonian motor symptoms, as well as neuroanatomical structures critical to this mechanism, have yet to be identified.

A frequently used animal model to study extrapyramidal motor dysfunctions is catalepsy, an abnormal rodent behavior resembling bradykinesia and postural rigidity in human parkinsonism. Catalepsy, as well as the PD-associated extrapyramidal signs, is linked to an inhibition of the central dopaminergic processes (Crocker and Hemsley, 2001; Wadenberg et al., 2001).

Experimental catalepsy can be produced by various drugs, among those are haloperidol, reserpine, and narcotic analgesics (e.g., Malec and Langwiński, 1983; Zarrindast et al., 1998, Zarrindast et al., 2002); and there is a growing body of evidence describing the mechanisms of such drug-induced catalepsy. Meanwhile, the relevance of data obtained from these studies to the etiology of human PD is questionable.

One of the PD-associated abnormalities is a fall in brain levels of somatostatin (for Refs., see Ionov and Pushinskaya, 2013). We have recently simulated this abnormality in Wistar rats (Ionov and Pushinskaya, 2013) using intracerebroventricular injections of a somatostatin receptor antagonist, cyclosomatostatin (cSST) (Fries et al., 1982). It has been found that cSST induces cataleptic response, and this effect was greater in aged than in young rats. Given that age represents the largest risk factor for the development of PD (Reeve et al., 2014), the cSST-induced catalepsy displayed the age-dependence similar to that of PD. Apparently, this property of the model supports its validity.

An important feature of the model is its responsiveness to clinically effective agents (Willner, 1984; Duty and Jenner, 2011). One

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of the potential antiparkinsonian agents may be nicotine since epidemiological studies have shown a lower risk of PD in tobacco smokers (Ascherio and Schwarzschild, 2016). The cSST-induced catalepsy has been found to be reversed by nicotine (Ionov and Pushinskaya, unpublished results). In this regard, the cSST catalepsy differs radically from the models using neuroleptics: nicotine potentiated rather than inhibited catalepsy induced by haloperidol (Sanberg et al., 1993) and some other drugs (Zarrindast et al., 1998, Zarrindast et al., 2002). The similarity between the cSST model and human PD in sensitivity to nicotine/smoking supports a role of somatostatin deficiency in human extrapyramidal dysfunctions.

The neuroanatomical substrates mediating the somatostatin antagonist-induced catalepsy are unknown. To expand the current knowledge regarding the involvement of somatostatinergic processes in brain functioning, we assessed the catalepsy-inducing effects of cSST injected into different brain regions. The SNc, DS, LC, pedunculopontine tegmental nucleus (PPTg), and inferior colliculus (IC) were tested. The presence of somatostatatin-containing neurons in all these brain areas (Palkovits et al., 1982; Douglas and Palkovits, 1982; Zoli et al., 1990; Giehl and Mestres, 1995; Rushlow et al., 1996; Wynne and Robertson, 1997) may point to an involvement of these anatomical structures in the central somatostatinergic processes and to a sensitivity of these structures to cSST.

To verify the role of the somatostatin receptor blockade in cSST-induced effects, cSST was combined with octreotide (OCT), a stable somatostatin receptor agonist (Ben-Shlomo et al., 2009).

2. Results

The brain sections were examined under a light microscope, and the location of injection cannula tips within the brain tissue was determined. In some of the animals, it was found that the microinjection sites were not located within the boundaries of the targeted area. The data from these animals were rejected. Representative photomicrographs of the microinjection sites within the targeted areas are presented in Fig. 1(A–E). After histological examination, eight animals in each operated group were selected for statistical analysis (see also Section 4.7). Fig. 2(A–E) shows the location of the injection cannula tips in animals included in the statistical analyses (note that the number of sites in this figure is less than the total number of rats used because several circles overlap).

The evaluation of catalepsy yielded the following results. The non-drug factors (surgical manipulations, vehicle intervention) *per se* did not influence the duration of immobility at all time points of observation. Differences between the unoperated and vehicle-treated rats were as follows: for intra-SNc injections, H = 4.12, $p = 0.40$ for 60 min, H = 4.39, $p = 0.48$ for 120 min, H = 4.19, $p = 0.51$ for 180 min, H = 4.57, $p = 0.46$ for 240 min; for intra-DS injections, H = 4.37, $p = 0.49$ for 60 min, H = 4.76, $p = 0.32$ for 120 min, H = 5.03, $p = 0.44$ for 180 min, H = 5.31, $p = 0.37$ for 240 min; for intra-LC injections, H = 4.24, $p = 0.41$ for 60 min, H = 4.88, $p = 0.47$ for 120 min, H = 4.18, $p = 0.52$ for 180 min, H = 4.54, $p = 0.43$ for 240 min; for intra-PPTg injections, H = 4.93, $p = 0.32$ for 60 min, H = 4.91, $p = 0.54$ for 120 min, H = 4.36, $p = 0.39$ for 180 min, H = 4.32, $p = 0.52$ for 240 min; for intra-IC injections, H = 4.18, $p = 0.53$ for 60 min, H = 4.02, $p = 0.45$ for 120 min, H = 4.89, $p = 0.43$ for 180 min, H = 4.98, $p = 0.44$ for 240 min (Figs. 3A–E and 4).

Intra-SNc administration of cSST at the dose of 0.05 μg did not produced a cataleptogenic effect (differences from the vehicle-treated control were as follows: H = 4.19, $p = 0.36$ for 60 min; H = 4.24, $p = 0.33$ for 120 min; H = 4.23, $p = 0.41$ for 180 min; H = 4.87, $p = 0.35$ for 240 min). Similarly, no effect was observed after intra-SNc administration of cSST at the dose of 0.2 μg (differences from the vehicle-treated control were as follows: H = 7.04, $p = 0.42$ for 60 min; H = 6.96, $p = 0.37$ for 120 min; H = 7.83, $p = 0.35$ for 180 min; H = 6.94, $p = 0.46$ for 240 min). In contrast, cSST at

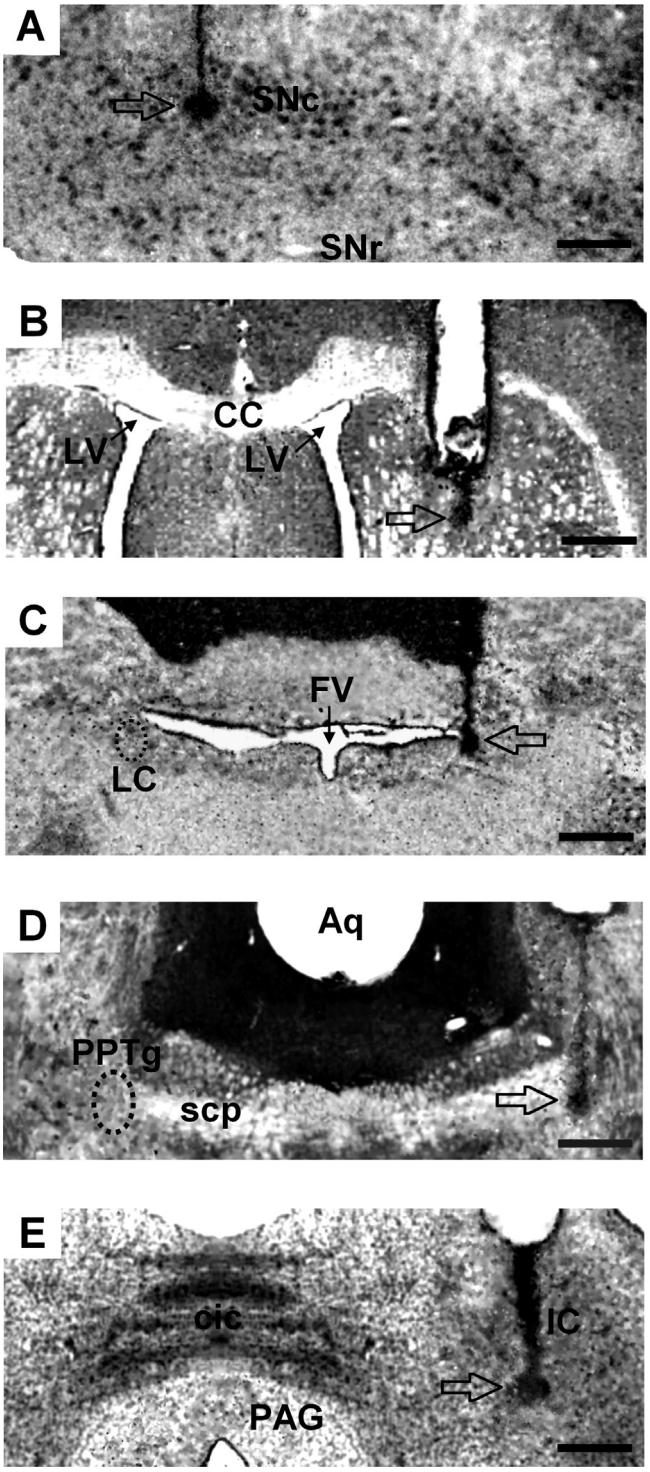

Fig. 1. Representative photomicrographs of the microinjection sites. Coronal sections through the substantia nigra pars compacta (A), dorsal striatum (B), locus coeruleus (C), pedunculopontine tegmental nucleus (D), inferior colliculus (E). (A) SNc – substantia nigra pars compacta, SNr – substantia nigra pars reticulata; (B) cc – corpus callosum, LV – lateral ventricle; (C) LC – locus coeruleus, FV – forth ventricle; (D) PPTg – pedunculopontine tegmental nucleus, Aq – aqueduct, scp – superior cerebellar peduncle; (E) IC – inferior colliculus, cic – commissure of the IC, PAG – periaqueductal gray. The clear arrow indicates the area of microinjection. Scale bar: 0.5 mm.