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Biperiden hydrochlorate ameliorates dystonia of rats produced by microinjection of sigma ligands into the red nucleus

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Abstract

It has been reported that the imbalance of anticholinergic and antidopaminergic activity of each neuroleptic drug correlates with the capacity to produce neuroleptic-induced acute dystonia (NAD) and the major focus of NAD is thought to be the striatum. Anticholinergic drugs are highly effective on NAD, but they are partially effective on neuroleptic-induced tardive dystonia and their effect on idiopathic dystonia is disappointing. Recently, it has been reported that the unilateral microinjection of sigma (σ) ligands into the red nucleus induces torticollis of rats. This animal model appears to be a model of dystonia, but it is not clear whether it is suitable for NAD in man. To clarify this issue, we investigated the effect of an anticholinergic drug, biperiden hydrochlorate (BH), on this animal model. This study revealed that BH dose-dependently ameliorated dystonia of rats induced by two σ ligands, whether each σ ligand had dopaminergic affinity or not. This animal model of dystonia appears to be a model of NAD in man from the viewpoint of treatment-response. The results also suggest that not only dopaminergic and cholinergic systems but also σ system, and not only the striatum but also the red nucleus, may play an important role in the pathophysiology of NAD.

Keywords: Neuroleptic-induced acute dystonia; Anticholinergic drugs; Sigma ligands; Red nucleus; Rats

1. Introduction

Neuroleptic-induced acute dystonia (NAD) is a major complication of treatment with neuroleptic drugs. Snyder et al. [20] reported that the imbalance of anticholinergic and antidopaminergic activity of each neuroleptic drug correlated with the capacity to produce NAD. Kolbe et al. [9] reported that the persisting compensatory dopamine (DA) release acting on unblocked emergingly supersensitive DA receptor after administration of neuroleptic drugs, particularly in the striatum, was responsible for NAD. More recently, sigma (σ) receptor, first identified as a binding site for (+)-*N*-allyl-normetazocine [(+)-SKF-10,047] [11,21,22], was thought to be involved in the regulation of movement and posture. The unilateral microinjection of haloperidol (HPD), which has high affinity for both DA D_2 and σ receptors, into the red nucleus induces neck dystonia of rats. 1,3-Di-*o*-tolyl-guanidine (DTG) has very low affinity for DA D_2 receptor and high affinity for σ receptor, but it also induces dystonia in the same way [23]. The behavioral potency of σ ligands in inducing neck dystonia of rats correlates well with their affinity for σ receptor [15]. Jeanjean et al. [4] reported that there was a correlation between the clinical incidence of NAD and binding affinity of neuroleptic drugs for σ receptor. These data suggest the possible involvement of σ receptor in the pathophysiology of NAD.

It is well known that anticholinergic drugs are highly effective on NAD, and almost 100% of NAD patients benefit from anticholinergic medications [7]. By contrast, they are partially effective on neuroleptic-induced tardive dystonia, and their effect on idiopathic dystonia is disappointing [6,10]. Biperiden hydrochlorate (BH) is one of the anticholinergic drugs most frequently prescribed in Japan, and it has also been reported to be effective on NAD and not to be effective on neuroleptic-induced tardive dystonia [12,13]. The torticollis of rats induced by microinjection of HPD or DTG into the red nucleus appears to be a model of dystonia in general, but it is not clear whether this animal

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model is suitable for NAD in man. To clarify this issue, we investigated the effect of BH on this animal model.

2. Materials and methods

The procedures involving animals and their care were conducted in conformity with institutional guidelines that are in compliance with the "Guide for Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985).

2.1. Animals and surgery

Male Wistar rats (250–350 g at the time of surgery) were used in this study. They were implanted with a transverse 21-gauge guide cannula (EiCOm, Kyoto, JAPAN) under pentobarbital anesthesia (50 mg/kg, IP). The guide cannula was stereotaxically placed to terminate 4.5 mm above the left red nucleus with the use of the atlas published by Paxinos and Watson [18] (A: +3.0 mm, L: +1.0 mm and V: −3.5 mm from the intraaural line and the skull surface), and was secured with dental cement and skull screws. It was enclosed with an imitation cannula except for the injection experiment. After surgery, the rats were housed individually in acrylic resin cages ($30 \times 30 \times 35$ cm) throughout the experiment, and were allowed free access to food and water.

2.2. Behavioral testing

The behavioral testing was carried out after at least a 24-h recovery period. DTG (5 mg/ml) or HPD (5 mg/ml) was dissolved in 0.25% acetic acid and injected into the red nucleus in a volume of 0.5 μl over 60 s through a 25-gauge injection cannula. Acetic acid (0.25%) was also microinjected into the red nucleus as a control ($n=6$). A 5% glucose solution ($n=6$) or BH (AKINETON parenteral solution diluted with 5% glucose solution, 2 or 0.5 mg/kg, $n=6$, 6) was intraperitoneally injected 30 min before microinjection of HPD or DTG. The rats' behavior was recorded on videotape. Torsional movements of the head (rotation around the sagittal axis) were quantified by measuring the angle of deviation of the head from the horizontal plane, using the eyes of the animals as a reference. Measurements were taken just before and 5, 10, 20, 40, and 60 min after microinjection. Each rat was tested only once to minimize damage to brain tissue. The position of the injection cannula was verified histologically by an examination of brain slice sections at the end of each experiment.

2.3. Statistical analysis

Statistical analysis was carried out using two-way repeated measures ANOVA to evaluate the difference in temporary changes, and one-way ANOVA followed by Fisher's PLSD post-hoc test for maximal head deviations.

3. Results

3.1. Effects of BH on neck dystonia induced by microinjection of DTG

Fig. 1 shows the time course of the deviation angle of neck dystonia. Intraperitoneal injection of BH dose-dependently suppressed neck dystonia induced by microinjection of DTG. Thus, 0.5 and 2.0 mg/kg BH significantly suppressed dystonia as compared to 5% glucose and 0.5 mg/kg BH, respectively (5% glucose vs. 0.5 mg/kg BH, $F=3.199$, $P=.0139$; 0.5 mg/kg BH vs. 2.0 mg/kg BH, $F=10.262$, $P<.0001$). The intensity of neck dystonia in the control group was less than that after the intraperitoneal injection of 2.0 mg/kg BH ($f=9.723$, $P<.0001$). Maximal deviations of neck dystonia were produced 10 min after microinjection of DTG and also showed dose-dependency. Thus, 0.5 and 2.0 mg/kg BH significantly lessened the maximal deviation as compared to 5% glucose and 0.5 mg/kg BH, respectively (5% glucose vs. 0.5 mg/kg, $P=.0012$; 0.5 mg/kg BH vs. 2.0 mg/kg BH; $P<.0001$). The maximal deviation of neck dystonia in the control group was smaller than that after the intraperitoneal injection of 2.0 mg/kg BH ($P<.0001$).

3.2. Effects of BH on neck dystonia induced by microinjection of HPD

Fig. 2 shows the time course of the deviation angle of neck dystonia. Intraperitoneal injection of BH dose-dependently suppressed neck dystonia induced by microinjection of HPD. Thus, 0.5 and 2.0 mg/kg BH significantly suppressed dystonia as compared to 5% glucose and 0.5 mg/kg BH, respectively (5% glucose vs. 0.5 mg/kg BH, $F=4.587$, $P=.0016$; 0.5 mg/kg BH vs. 2.0 mg/kg BH, $F=24.478$, $P<.0001$). The intensity of neck dystonia in the control group was less than that after the intraperitoneal injection of 2.0 mg/kg BH ($f=21.153$, $P<.0001$). Maximal deviations of neck dystonia were produced 10 min after micro-

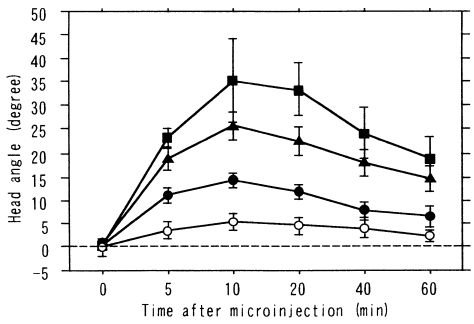

Fig. 1. Time course of neck dystonia induced by microinjection of DTG. 5% glucose (■), 0.5 (▲) and 2.0 mg/kg BH (●) were intraperitoneally injected 30 min before microinjection (○: control). Each point represents the mean (±S.D.) degrees from the horizontal plane.

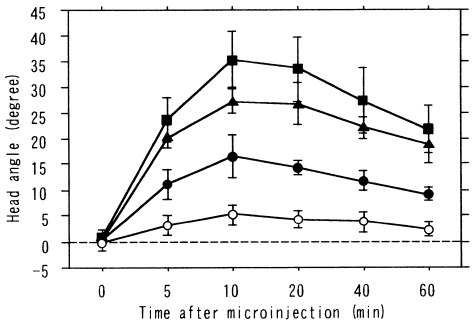

Fig. 2. Time-course of neck dystonia induced by microinjection of HPD. 5% glucose (■), 0.5 (▲) and 2.0 mg/kg BH (●) were intraperitoneally injected 30 min before microinjection (○: control). Each point represents the mean (±S.D.) degrees from the horizontal plane.

injection of HPD and also showed dose-dependency. Thus, 0.5 and 2.0 mg/kg BH significantly lessened the maximal deviation as compared to 5% glucose and 0.5 mg/kg BH, respectively (5% glucose vs. 0.5 mg/kg BH, $P = .0029$; 0.5 mg/kg BH vs. 2.0 mg/kg BH, $P = .0004$). The maximal deviation of neck dystonia in the control group was smaller than that after the intraperitoneal injection of 2.0 mg/kg BH ($P = .0049$).

4. Discussion

The present study showed that intraperitoneal injection of BH dose-dependently suppressed neck dystonia of rats produced by unilateral microinjection of DTG or HPD into the red nucleus. Both HPD and DTG have high affinity for σ receptor, while HPD has high affinity for DA receptor and DTG has very low affinity for DA receptor. The suppressing effect on dystonia of BH was almost equal whether or not the dystonia-inducing compounds had dopaminergic affinity. Previous studies have revealed that anticholinergic drugs are highly effective on NAD, while they are partially effective on tardive dystonia and their effect on idiopathic dystonia is disappointing [6,7,10]. From the viewpoint of treatment-response, this animal model appears to be suitable for NAD in man.

It has been hypothesized that dopaminergic and cholinergic systems are involved in the pathophysiology of NAD and its major focus is the striatum [9,20], but the pathophysiology of NAD is still not clear. Jeanjean et al. [4] reported that the incidence of NAD correlated the affinity for σ receptor of each neuroleptic drug. Anatomically, the highest concentrations of σ receptor occur in brain areas involved in the control of movement and posture, particularly in the cerebellum, red nucleus, superior colliculus, spinal ventral horn and various cranial nerve nuclei (facial, hypoglossal and motor trigeminal) [3,11,17]. The red nucleus receives its major input from the nucleus interpositus of the cerebellum, and projects efferently to the intermediate levels of the spinal cord, the nucleus interpositus and the lateral reticular nucleus [1,2,14,19]. These anatomical findings suggest that σ receptor have a function in the regulation of movement and posture in areas of the face, neck and upper part of the body. NAD is most often localized in these parts of the body [4], and this distribution corresponds to the high concentration area of σ receptor. Taking these things together, it seems that not only dopaminergic and cholinergic systems but also the σ system, and not only the striatum but also the red nucleus, are involved in the pathophysiology of NAD.

Based on the hypothesis of Snyder et al. [20], anticholinergic drugs are thought to be effective on NAD through compensating dopaminergic and cholinergic imbalance. However, the suppressing effect of BH on DTG-induced dystonia cannot be explained by the above mechanism. One possible explanation for this effect is that BH has affinity for σ receptor and directly antagonizes DTG. There have been no reports about the affinity of BH for σ receptor, and we cannot affirm or deny this explanation. Another explanation is the interaction between the σ and cholinergic systems. Junien et al. [5] reported that σ compounds displayed differential effects on evoked acetylcholine (ACh) release in rat hippocampal slice preparations, and Matsuno et al. [16] reported that DTG dose-dependently increased extracellular ACh levels in the frontal cortex of rats. These studies indicate the possibility that BH ameliorates dystonia of rats induced by microinjection of DTG through the interaction between σ and cholinergic systems, and BH may be effective on DTG-induced dystonia by counteracting the increased ACh release. Kobayashi et al. [8] reported that (+)-SKF-10,047 and DTG increased the extracellular ACh level in the hippocampus, while the striatal extracellular ACh level was slightly affected by (+)-SKF-10,047 and was not affected by DTG. This regional difference suggests that the interaction between σ and cholinergic systems may be a minimum in the striatum, which was formerly thought to be the major focus of NAD. The details of this interaction are unclear, because BH was administered systemically in this study.

We revealed that BH ameliorated dystonia of rats induced by microinjection of two σ ligands, DTG and HPD, whether or not each σ ligand had dopaminergic affinity. This animal model of dystonia appears to be a model of NAD in man from the viewpoint of treatment-response, and not only dopaminergic and cholinergic systems but also σ system, and not only the striatum but also the red nucleus, may play an important role in the pathophysiology of NAD. Information about the affinity of BH and other anticholinergic drugs for sigma receptors is useful to ascertain whether their antidystonic effects are mediated through anticholinergic actions or through sigma receptor antagonism, but there is no available data reported at the moment. The affinity of anticholinergic drugs for sigma receptors should be examined, and it would greatly clarify the relationship between the various mechanisms described in the present study.

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