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Receptor fingerprinting the circling *ci2* rat mutant: Insights into brain asymmetry and motor control

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Abstract

Circling behaviour of the *ci2* rat mutant, a model for hyperkinetic movement disorders, is associated with an abnormal asymmetry in striatal dopaminergic activity. Since it is more likely that imbalances in several neurotransmitter systems result in the cascade of neurochemical disturbances underlying disorders involving motor dysfunctions, we measured the densities of 12 neurotransmitter receptors in the basal ganglia and vestibular nuclei of adult circling mutants (*ci2*/*ci2*), non-circling littermates (*ci2*/+) and controls from the background strain (LEW/Ztm). In controls, the left caudate putamen (CPu) contains lower kainate and the left globus pallidus higher AMPA densities than their right counterparts. The medial vestibular nucleus of mutants ipsilateral to the preferred direction of rotation contained higher M_2 densities than the contralateral one. *ci2*/+ animals presented no interhemispheric differences, did not differ behaviourally from controls, but contained lower $GABA_A$ densities in the CPu, nucleus accumbens (Acb) and reticular (Rt), ventromedial (VM) and ventral posterolateral (VPL) thalamic nuclei. Mutants contained lower $GABA_A$ (CPu, Acb, Rt, VPL) but higher nicotinic (Rt, VM) densities than controls and higher $GABA_A$ (CPu, VM) densities than *ci2*/+ rats. Hyperactivity level of mutants was positively correlated with the adenosine A_{2A} receptor densities in the ipsilateral Acb, but negatively correlated with those of the ipsilateral thalamus. Concluding, *ci2*/*ci2* mutants show alterations in $GABA_A$, cholinergic and A_{2A} receptor densities. Our data add to the hypothesis that motor disorders such as hyperkinesias cannot be explained solely by absolute functional increases or decreases in the dopaminergic system, but are due to imbalances in several neurotransmitter systems.
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Keywords: Movement disorders; Neurotransmitter receptors; Receptor autoradiography

Introduction

The *ci2* rat mutant, which was first described in 1996 (Löscher et al., 1996), is characterized by abnormal lateralized circling, deafness, progressive retinopathy, locomotor hyperactivity, opisthotonus ("stargazing"), ataxia, and swimming inability (Chwalisz et al., 2003; Löscher et al., 1996; Lindemann et al., 2001; Kaiser et al., 2001; Richter et al., 1999; Fedrowitz et al., 2003). The phenotype is caused by a spontaneous autosomal recessive mutation (homozygous *ci2*/*ci2*) and was discovered in a Lewis (Lew/Ztm) rat breeding colony at the Central Institute for Laboratory Animal Breeding in Hannover (Löscher et al., 1996). Investigations of vestibular and auditory functions revealed that *ci2*/*ci2* rats are deaf and exhibit a virtually complete loss of the cochlear neuroepithelium, while more discrete defects were seen in the vestibular neuroepithelium (Kaiser et al., 2001). Furthermore, a progressive retinitis pigmentosa, leading to a progressive reduction of light-evoked retinal responses, was also determined in this mutant (Gockeln et al., 2003). The combination of neurological, auditory and retinal defects observed in *ci2*/*ci2* rats

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led us to propose that these animals may provide a model for the Usher syndrome, the most common form of deaf–blindness in humans (Kremer et al., 2006). In contrast to homozygous *ci2*/*ci2* rats, heterozygous littermates (*ci2*/+) do not display any of the above described abnormal behavioural patterns, nor are they deaf, although they may loose sight in adulthood (Gockeln et al., 2003).

Neurochemical studies revealed that homozygous *ci2* rats have a lower tissue concentration of dopamine and its metabolites in the striatum ipsilateral to the preferred direction of rotation (Löscher et al., 1996; Richter et al., 1999), which is in line with the general observation that rats turn away from the brain hemisphere with higher striatal dopaminergic activity (Carlson and Glick, 1996). Additionally, *ci2*/*ci2* rats exhibit an asymmetric, contralateral, increase in striatal dopamine release during stress-induced circling behaviour (Fedrowitz et al., 2000) which can be inhibited by the D_2 receptor antagonist raclopride (Schirmer et al., 2007). However, these differences are not accompanied by dopaminergic cell loss or by hemispheric imbalances in the substantia nigra (Richter et al., 1999). The substantia nigra and the striatum of *ci2*/*ci2* rats do not present asymmetries regarding their D_1 and D_2 receptor densities or their content of dopamine transporter either, although the striatum of *ci2*/*ci2* rats contains a higher density of D_1 receptors and of dopamine transporter than that of control rats and the substantia nigra of *ci2*/*ci2* rats contains a higher density of D_1 and D_2 receptors than that of control rats (Richter et al., 1999).

Additionally, bilateral recordings of spontaneous extracellular single unit activity of GABAergic neurons in the striatum of *ci2*/*ci2* rats did not reveal significant hemispheric imbalances in neuronal firing rate or pattern, nor were there activity differences between *ci2*/*ci2* and control rats (Fedrowitz et al., 2003). Although neurons in the substantia nigra of *ci2*/*ci2* rats did not present interhemispheric differences in activity either, their mean spontaneous discharge rate was significantly higher and more synchronous than that of neurons in control rats (Fedrowitz et al., 2003).

Neurotransmitter receptors are not found in isolated form in the brain. Since a single neuron may express a variety of receptor subtypes for different neurotransmitter systems, a single architectonical area will contain many different receptor subtypes. Furthermore, there is a functional interaction between neurotransmitter systems, so that synaptic signalling mediated by a given neurotransmitter can be altered as a consequence of previous alterations in other neurotransmitter systems (Zilles et al., 2002b). Imbalances in several neurotransmitter systems, and not just absolute functional increases or decreases in a single system are thought to play a key role in the cascade of neurochemical disturbances which underlie disorders involving motor dysfunctions such as Huntington's chorea (Yakimovskii and Varshavskaya, 2004), Tourette syndrome (Mink, 2006), Parkinson's disease (Chase and Oh, 2000), and schizophrenia (Carlson and Glick, 1996).

The *ci2* rat mutant constitutes an established model for hyperkinetic movement disorders and it is thought that imbalances in nigrostriatal dopaminergic activity are not the sole cause of the abnormal behaviour of *ci2*/*ci2* rats (Richter et al., 1999). Rather, several neurotransmitter systems in addition to dopamine might contribute to the control of locomotion. Thus, in the present study we applied quantitative *in vitro* receptor autoradiography to determine the mean densities of receptors for the classical neurotransmitters glutamate, GABA, acetylcholine, noradrenaline and serotonin, as well as of the neuromodulator adenosine in diverse structures of the basal ganglia circuitry and vestibular nuclei of *ci2*/*ci2* rats and compared them to those obtained in heterozygous *ci2*/+ and in wild type rats of the background strain (Lew/Ztm).

Material and methods

Animals

The mutant *ci2* rat (homozygous *ci2*/*ci2*) was isolated in F96 of LEW/Han rats and is being maintained as a segregated inbred strain LEW/Ztm-*ci2* at the Central Animal Facility of the Hannover Medical School, Germany (Löscher et al., 1996). About 50% of the offspring exhibit the mutation (*ci2*/*ci2*), which can be identified by phenotype behaviour (intense circling, hyperactivity, ataxia, opisthotonus) as early as 10–14 days of age, while the remaining 50% of pups are unaffected (*ci2*/+), showing normal behaviour. This makes them suitable experimental controls for comparing behavioural differences. Normal rats of the genetic background strain (LEW/Ztm, wild type rats) were used as additional controls for comparison with the mutant homozygous rats.

The present studies involved a total of 8 homozygous LEW/Ztm *ci2*/*ci2* rat mutants (*ci2*/*ci2* rats), 8 heterozygous LEW/Ztm *ci2*/+ littermates (*ci2*/+ rats), and 8 LEW/Ztm (WT) rats. All rats were males and age-matched. After weaning, rats were housed alone and kept under controlled environmental conditions (room temperature 24–25 °C, humidity 50–60%, 12/12 h light/dark cycle, lights on at 6.00 a.m.). Standard laboratory chow (Altromin 1324 standard diet) and tap water were allowed *ad libitum*. All behavioural tests were performed during the light period of the light–dark cycle. All possible steps were taken to avoid the animals' suffering at each stage of the experiment. The

Table 1
Tritiated ligands used to label the examined receptors

Neurotransmitter	Receptor	Ligand
Glutamate	AMPA	[^{3}H] AMPA
	Kainate	[^{3}H] kainate
	NMDA	[^{3}H] MK-801
GABA	$GABA_A$	[^{3}H] muscimol
	$GABA_B$	[^{3}H] CGP-54626
	BZ	[^{3}H] flumazenil
Acetylcholine	M_1	[^{3}H] pirenzepine
	M_2	[^{3}H] oxotremorine-M
	M_3	[^{3}H] 4-DAMP
	N	[^{3}H] epibatidine
Epinephrine	α_1	[^{3}H] prazosin
	α_{2h}	[^{3}H] UK-14,304
Serotonin	5-HT_2	[^{3}H] ketanserin
Adenosine	A_1	[^{3}H] DPCPX
(Neuromodulator)	A_{2A}	[^{3}H] ZM241385

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