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Original Article

Occurrence of Spontaneous Tumors in the Central Nervous System (CNS) of F344 and SD Rats

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Abstract: In order to accurately assess the carcinogenicity of chemicals with regard to rare tumors such as rat CNS tumors, sufficient information about spontaneous tumors are very important. This paper presents the data on the type, incidence and detected age of CNS tumors in F344/DuCrlCrlj (a total of 1363 males and 1363 females) and Crl:CD(SD) rats (a total of 1650 males and 1705 females) collected from in-house background data-collection studies and control groups of carcinogenicity studies at our laboratory, together with those previously reported in F344 and SD rats. The present data on F344/DuCrlCrlj rats (F344 rats) and Crl:CD(SD) rats (SD rats) clarified the following. (1) The incidences of all CNS tumors observed in F344 rats were less than 1%. (2) The incidences of malignant astrocytoma and granular cell tumor were higher in male SD rats than in female SD rats. (3) The incidences of astrocytoma and granular cell tumor were higher in SD rats than in F344 rats. (4) Among astrocytoma, oligodendroglioma and granular cell tumor, oligodendroglioma was detected at the youngest age, followed by astrocytoma, and ultimately, granular cell tumor developed in both strains. The incidences observed in our study were almost consistent with those previously reported in F344 and SD rats. (DOI: 10.1293/tox.26.263; J Toxicol Pathol 2013; 26: 263–273)

Key words: historical control data, central nervous system tumor, F344 rat, SD rat

Introduction

Although there is no adequate information about spontaneous tumors in the rat central nervous system (CNS), certain types of tumors induced by N-nitrosoalkylureas in the rat CNS suggest a possibility of occurrence of similar tumors in the human CNS exposed to such chemicals[1].

In the nearly 500 carcinogenicity reports of the National Toxicology Program (NTP), 10 compounds showed evidence of an increase in brain tumors. Within the 10 compounds, only glycidol clearly induced brain tumors in rats. The other 9 compounds were considered equivocal. Because statistically significant increased incidences, decreased survival and dose-response relationships were not observed, and several factors (such as the carcinogenicity evidence at other sites, mutagenicity, increases in malignant type, no brain neoplasms in concurrent controls or increased brain tumors in structurally related chemicals) supported the theory that marginal increases in brain tumor incidence were related to chemical exposure[2]. This indicates a difficulty in accurately evaluating chemical-related CNS tumors in a carcinogenicity study. This is probably due to a low incidence of CNS tumors even in a carcinogenicity study, and what is worse, it is probably also due to insufficient data on spontaneous tumors in the rat CNS. Therefore, more extensive data on the occurrence of rat CNS tumors are required[3, 4]. In this regard, data obtained from the same laboratory are thought to be valuable as historical control data (HCD)[5], because it is said that diet[6] and housing condition[6, 7] probably influence the occurrence of tumors. In addition, it is important to survey the previously reported data in detail because rat CNS tumors are generally rare.

This paper presents the data on the occurrence of CNS tumors obtained from the in-house background data-collection studies and carcinogenicity studies at our laboratory, together with those previously reported in F344 and SD rats[9–22]. In addition, some biological features of rat CNS tumors such as the age of tumor occurrence were also examined.

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Materials and Methods

Regarding the F344/DuCrlCrlj rats (Charles River Laboratories Japan, Inc., Atsugi, Kanagawa, Japan), a total of 1363 males and 1363 females, which were obtained from 2 background data-collection studies and from control groups of 17 carcinogenicity studies, were examined. All studies started between 1991 and 2009. Except for the background data-collection studies, each carcinogenicity study had one or two control groups, and there were a total of 23 groups.

Regarding the Crl:CD(SD) rats (Charles River Laboratories Japan, Inc.), a total of 1650 males and 1705 females, which were obtained from 3 background data-collection studies in both sexes and from control groups of 22 and 23 carcinogenicity studies in males and females, respectively, were examined. All studies started between 1996 and 2009. Except for the background data-collection studies, each carcinogenicity study had one or two control groups, and the data consisted of 28 male groups and 29 female groups.

All studies were conducted in compliance with laws and guidelines concerning animal welfare such as the Law for the Humane Treatment and Management of Animals (Law No. 105), Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain (Notification No. 88 of the Ministry of the Environment, Japan), Guidelines for Proper Conduct of Animal Experiments (Scientific Council of Japan) and the Guide for Animal Care and Use of our facility.

Animals were housed individually in bracket-type stainlesssteel wire mesh cages and were maintained in a barrier-sustained room controlled at 23 ± 3°C and 50 ± 20% relative humidity, with air ventilation at 10 to 15 times per hour and artificial lighting for 12 hours per day. The animals were allowed free access to CRF-1 diet (Oriental Yeast Co., Ltd, Tokyo, Japan) and tap water.

All sections of CNS tissues with tumors were reviewed according to the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND)[8].

Results

Incidence of CNS tumors

The occurrence of CNS tumors in individual groups is shown in Table 1 (F344/DuCrlCrlj male rats), Table 2 (F344/DuCrlCrlj female rats), Table 3 (Crl:CD(SD) male rats) and Table 4 (Crl:CD(SD) female rats).

In the F344/DuCrlCrlj rats, malignant astrocytoma, malignant oligodendroglioma, malignant mixed glioma, medulloblastoma, granular cell tumor, malignant meningioma, osteosarcoma and malignant reticulosis were observed, and the incidences of these tumors were very low (one or two tumors/group in a small number of groups).

In the Crl:CD(SD) rats, malignant astrocytoma, malignant oligodendroglioma, granular cell tumor, benign/malignant meningioma, osteosarcoma, malignant reticulosis and hemangioma were observed. A maximum of 4 cases of malignant astrocytoma per group were detected in a small number of groups, but the incidences of other tumors were very low (one or two tumors/group in a small number of groups).

In both F344/DuCrlCrlj and Crl:CD(SD) rats, as shown in Tables 1–4, although the vehicles and administration routes varied among the groups, the incidence of every tumor was not influenced by the differences in vehicles and administration routes. In addition, there were no time-related changes in the incidences of any types of tumors in F344/DuCrlCrlj and Crl:CD(SD) rats during 1991 to 2009 and 1996 to 2009, respectively.

The incidences of CNS tumors in F344/DuCrlCrlj and Crl:CD(SD) rats in the present study are shown in Table 5. In F344/DuCrlCrlj rats, the incidences of tumors were unexceptionally less than 1%. On the other hand, in Crl:CD(SD) rats, malignant astrocytoma was most common, and its incidence was more than 1%, while the incidences of tumors of other types were less than 1%. Among them, granular cell tumor was common next to malignant astrocytoma, and the incidences of malignant astrocytoma and granular cell tumor were higher in males than in females. In addition, the incidences of malignant astrocytoma and granular cell tumor were higher in Crl:CD(SD) rats than in F344/DuCrlCrlj rats.

Ages (days) when CNS tumors were detected

The ages (days) of rats when malignant astrocytoma, oligodendroglioma and granular cell tumor were detected are shown in Table 6.

Among these 3 types of tumors, malignant oligodendroglioma was detected at the youngest age, followed by malignant astrocytoma, and ultimately, granular cell tumor developed in both F344/DuCrlCrlj and Crl:CD(SD) rats. None of these 3 types of tumors developed earlier in F344/DuCrlCrlj rats than in Crl:CD(SD) rats.

The distributions of ages when these 3 types of tumors were detected are shown in Fig. 1 (F344/DuCrlCrlj rats) and Fig. 2 (Crl:CD(SD) rats). These 3 types of tumors generally occurred sparsely throughout the detected period in both F344/DuCrlCrlj and Crl:CD(SD) rats, although malignant astrocytoma in Crl:CD(SD) rats was frequently observed at an age of more than 600 days.

The previous reports of rat brain tumors

The cumulative incidences of rat brain tumors obtained from the present study and cited from the previous reports of HCD are shown in Table 7 (F344 rats) and Table 8 (SD rats).

In the previous reports, F344 rats included those of the F344/CrlBR, F344, F344/DuCrj, F344/NTac and F344/N strains, and SD rats included those of the Crj:SD(IGS), Crl:SDBR, Crl:SDBR(IGS), Crj:SD, Crl:SD and Hsd:SD strains. In the previously reported HCD, the incidences of all types of tumors were less than 1% in F344 rats, while the incidences of astrocytoma, oligodendroglioma, granular cell tumor and/or meningioma were sometimes or rarely more than 1% in SD rats. The incidences of astrocytoma

Table 1. The Occurrence of CNS Tumors by Study Group for F344/DuCrlCrlj Rats (Male)

Study ID:	#1	#2	#3	#3	#4	#4	#5	#6	#7	#8	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	#18	#19	Total	Mean (%)	Range (%)
Year study started:	1991	1992	1992	1992	1993	1993	1993	1993	1993	1994	1994	1994	1995	1997	2000	2000	2003	2003	2004	2005	2008	2008	2009			
Route of administration:	FD	FD	UT	FD	IV	UT	FD	FD	FD	GA	UT	FD	PC	GA	GA	GA	GA	GA	SC	FD	PO	PO	GA			
Vehicle*:	BD	BD		ST	ST		BD	BD	BD	MC		BD	ST	MC	DW	DW	MC	TG	GL	BD	DW	ST	MC			
Number of animals:	50	238	50	50	50	50	50	50	50	55	55	20	50	55	55	55	55	55	55	50	55	55	55	1363		
Brain																										
Astrocytoma, malignant	0	0	0	0	0	1	0	0	0	0	0	0	2	0	1	2	0	0	0	0	2	0	0	8	0.6	0–4.0
Oligodendroglioma, malignant	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	4	0.3	0–2.0
Glioma, mixed, malignant	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	0.1	0–2.0
Tumor, granular cell	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	0.1	0–1.8
Meningioma, malignant	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	0.1	0–1.8
Osteosarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0.1	0–2.0
Reticulosis, malignant	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.8
Spinal cord																										
Astrocytoma, malignant	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–0.0
Brain+spinal cord																										
Astrocytoma, malignant	0	0	0	0	0	1	0	0	0	0	1	0	2	0	1	2	0	0	0	0	2	0	0	9	0.7	0–4.0
Oligodendroglioma, malignant	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	4	0.3	0–2.0
Glioma, mixed, malignant	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	0.1	0–2.0
Tumor, granular cell	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	0.1	0–1.8
Meningioma, malignant	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	0.1	0–1.8
Osteosarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0.1	0–2.0
Reticulosis, malignant	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.8

FD, UT, IV, GA, PC, SC, BD, MC, DW, TG, GL and ST represent feeding, untreated, intravenous, gavage, percutaneous, subcutaneous, basal diet, methylcellulose, distilled water, powdered tragacanth, glucose and special for the study, respectively.

Table 2. The Occurrence of CNS Tumors by Study Group for F344/DuCrlCrlj Rats (Female)

Study ID:	#1	#2	#3	#3	#4	#4	#5	#6	#7	#8	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	#18	#19	Total	Mean (%)	Range (%)
Year study started:	1991	1992	1992	1992	1993	1993	1993	1993	1993	1994	1994	1994	1995	1997	2000	2000	2003	2003	2004	2005	2008	2008	2009			
Route of administration:	FD	FD	UT	FD	IV	UT	FD	FD	FD	GA	UT	FD	PC	GA	GA	GA	GA	GA	SC	FD	GA	GA	GA			
Vehicle:	BD	BD		ST	ST		BD	BD	BD	MC		BD	ST	MC	DW	DW	MC	TG	GL	BD	DW	ST	MC			
Number of animals:	50	238	50	50	50	50	50	50	50	55	55	20	50	55	55	55	55	55	55	50	55	55	55	1363		
Brain																										
Astrocytoma, malignant	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0.2	0–2.0
Oligodendroglioma, malignant	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	3	0.2	0–2.0
Medulloblastoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0.1	0–1.8
Reticulosis, malignant	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–2.0
Spinal cord																										
Astrocytoma, malignant	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0.1	0–1.8
Brain+spinal cord																										
Astrocytoma, malignant	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	4	0.3	0–2.0
Oligodendroglioma, malignant	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	3	0.2	0–2.0
Medulloblastoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0.1	0–1.8
Reticulosis, malignant	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–2.0

FD, UT, IV, GA, PC, SC, BD, MC, DW, TG, GL and ST represent feeding, untreated, intravenous, gavage, percutaneous, subcutaneous, basal diet, methylcellulose, distilled water, powdered tragacanth, glucose and special for the study, respectively.

Table 3. The Occurrence of CNS Tumors by Study Group for Crl:CD(SD) Rats (Male)

Study ID:	#1	#2	#3	#4	#4	#5	#6	#7	#8	#9	#9	#10	#11	#13	#14	#15	#16	#17	#18	#19	#20	#21	#22	#23	#24	#25	#26	#26	Total	Mean (%)	Range (%)
Year study started:	1996	1996	1998	1999	1999	2001	2001	2003	2003	2004	2004	2004	2005	2005	2005	2006	2007	2007	2007	2008	2006	2008	2008	2008	2008	2008	2009	2009			
Route of administration:	UT	UT	FD	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	FD	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA			
Vehicle:			BD	MC	MC	MC	MC	MC	TG	DW	ST	MC	DW	MC	DW	MCT	BD	AG	MC	MC	MC	MC	MC	DW	MC	MC	DW	ST			
Number of animals:	50	50	75	60	60	60	60	60	50	60	60	60	55	60	55	60	60	55	60	60	60	60	70	60	60	60	55	55	1650		
Brain																															
Astrocytoma, malignant	0	0	3	2	1	3	2	1	2	2	1	0	0	0	1	1	1	1	0	0	0	2	2	4	2	0	0	2	33	2.0	0–6.7
Oligodendroglioma, malignant	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	1	0	0	0	0	1	0	6	0.4	0–2.0
Tumor, granular cell	0	1	2	0	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0	0	1	1	1	0	1	0	0	0	11	0.7	0–2.7
Meningioma, benign	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Meningioma, malignant	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0.1	0–1.7
Osteosarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0.1	0–1.7
Reticulosis, malignant	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Spinal cord																															
Astrocytoma, malignant	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.3
Oligodendroglioma, malignant	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Brain+Spinal cord																															
Astrocytoma, malignant	0	0	4	2	1	3	2	1	2	2	1	0	0	0	1	1	1	1	0	0	0	2	2	4	2	0	0	2	34	2.1	0–6.7
Oligodendroglioma, malignant	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	1	0	0	0	0	1	0	7	0.4	0–2.0
Tumor, granular cell	0	1	2	0	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0	0	1	1	1	0	1	0	0	0	11	0.7	0–2.7
Meningioma, benign	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Meningioma, malignant	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0.1	0–1.7
Osteosarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0.1	0–1.7
Reticulosis, malignant	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7

T, FD, GA, BD, MC, TG, DW, ST, MCT and AG represent untreated, feeding, gavage, basal diet, methylcellulose, powdered tragacanth, distilled water, special for the study, ethanol containing Miglyol and gum arabic, respectively.

Table 4. The Occurrence of CNS Tumors by Study Group for Crl:CD(SD) Rats (Female)

Study ID:	#1	#2	#3	#4	#4	#5	#6	#7	#8	#9	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19	#20	#21	#22	#23	#24	#25	#26	#26	Total	Mean (%)	Range (%)
Year study started:	1996	1996	1998	1999	1999	2001	2001	2003	2003	2004	2004	2004	2005	2005	2005	2005	2006	2007	2007	2007	2008	2006	2008	2008	2008	2008	2008	2009	2009			
Route of administration:	UT	UT	FD	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	FD	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA	GA			
Vehicle:			BD	MC	MC	MC	MC	MC	TG	DW	ST	MC	DW	DW	MC	DW	MCT	BD	AG	MC	MC	MC	MC	MC	DW	MC	MC	DW	ST			
Number of animals:	50	50	75	60	60	60	60	60	50	60	60	60	55	55	60	55	60	60	55	60	60	60	60	70	60	60	60	55	55	1705		
Brain																																
Astrocytoma, malignant	0	0	0	0	0	0	0	1	0	3	0	1	0	2	0	0	0	1	0	1	0	1	0	2	2	0	1	3	1	19	1.1	0–5.0
Oligodendroglioma, malignant	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	3	0.2	0–1.8
Tumor, granular cell	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	3	0.2	0–3.3
Hemangioma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Spinal cord																																
Astrocytoma, malignant	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Meningioma, malignant	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Brain+Spinal cord																																
Astrocytoma, malignant	0	0	0	0	0	1	0	1	0	3	0	1	0	2	0	0	0	1	0	1	0	1	0	2	2	0	1	3	1	20	1.2	0–5.0
Oligodendroglioma, malignant	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	3	0.2	0–1.8
Tumor, granular cell	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	3	0.2	0–3.3
Meningioma, malignant	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7
Hemangioma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	0–1.7

UT, FD, GA, BD, MC, TG, DW, ST, MCT and AG represent untreated, feeding, gavage, basal diet, methylcellulose, powdered tragacanth, distilled water, special for the study, ethanol containing Miglyol and gum arabic, respectively.

Table 5. Incidence of CNS Tumors in F344/DuCrlCrlj and Crl:CD(SD) Rats

Strain:	F344		SD	
Sex:	Male	Female	Male	Female
Year study started:	1991-2009	1991-2009	1996-2009	1996-2009
Number of animals:	1363	1363	1650	1705
Brain				
Astrocytoma, malignant	0.6	0.2	2.0	1.1
Oligodendroglioma, malignant	0.3	0.2	0.4	0.2
Glioma, mixed, malignant	0.1	0	0	0
Medulloblastoma	0	0.1	0	0
Tumor, granular cell	0.1	0	0.7	0.2
Meningioma, benign	0	0	0.1	0
Meningioma, malignant	0.1	0	0.1	0
Osteosarcoma	0.1	0	0.1	0
Reticulosis, malignant	0.1	0.1	0.1	0
Hemangioma	0	0	0	0.1
Spinal cord				
Astrocytoma, malignant	0.1	0.1	0.1	0.1
Oligodendroglioma, malignant	0	0	0.1	0
Meningioma, malignant	0	0	0	0.1
Brain+Spinal cord				
Astrocytoma, malignant	0.7	0.3	2.1	1.2
Oligodendroglioma, malignant	0.3	0.2	0.4	0.2
Glioma, mixed, malignant	0.1	0	0	0
Medulloblastoma	0	0.1	0	0
Tumor, granular cell	0.1	0	0.7	0.2
Meningioma, benign	0	0	0.1	0
Meningioma, malignant	0.1	0	0.1	0.1
Osteosarcoma	0.1	0	0.1	0
Reticulosis, malignant	0.1	0.1	0.1	0
Hemangioma	0	0	0	0.1

Numbers in the table indicate incidences (%).

Table 6. Age at Detection of CNS Tumors in F344/DuCrlCrlj and Crl:CD(SD) Rats

Strain:	F344/DuCrlCrlj				Crl:CD(SD)			
Sex:	Male		Female		Male		Female	
Number of animals:	1363		1363		1650		1705	
	Total*	Range (days**)	Total	Range (days)	Total	Range (days)	Total	Range (days)
Brain + Spinal cord								
Astrocytoma, malignant	9	589–772	4	616–773	34	371–773	20	350–771
Oligodendroglioma, malignant	4	538–772	3	290–776	7	212–772	3	677–721
Tumor, granular cell	2	771–772	0		11	684–773	3	752–773

* Number of tumors, ** Detected age.

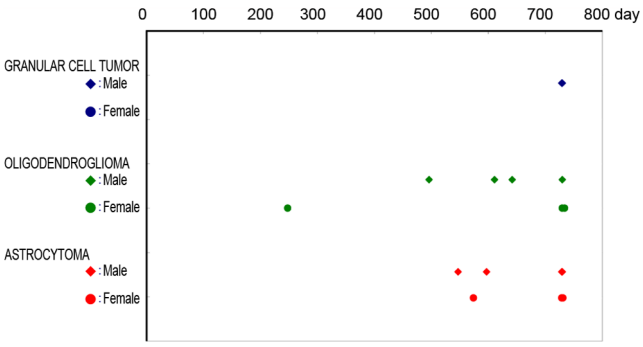

Fig. 1. Distribution of age at detection of malignant astrocytoma, malignant oligodendroglioma and granular cell tumor in F344/DuCrlCrlj rats.

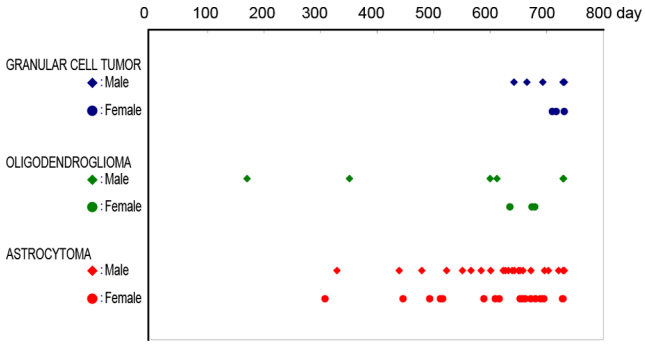

Fig. 2. Distribution of age at detection of malignant astrocytoma, malignant oligodendroglioma and granular cell tumor in Crl:CD(SD) rats.

Table 7. Cumulative Incidences of Spontaneous Brain Tumors in F344 Rats

	F344/DuCrj Present study		F344/CrlBR Charles River Lab. 1990[9]		F344 Haseman *et al.* 1990[10]		F344/DuCrj Iwata *et al.* 1991[11]		F344 Haseman *et al.* 1998[12]		F344/NTac Dinse *et al.* 2010[13]	F344/N NTP 2011[14]	
	M	F	M	F	M	F	M	F	M	F	F	M	F
Glial tumors													
Astrocytoma	0.6	0.2	0.7	0.5	0.5	0.9	0.1	0.1	0.4	0.3		0.2	0.0
Oligodendroglioma	0.3	0.2	0.2	0.1	0.1	0.2	0.0	0.1	0.4	0.3	0.2	0.2	0.3
Mixed glioma	0.1	0.0											
Glioma			0.1	0.1			0.3	0.0	0.1	0.3		0.0	0.3
Mixed glioma or glioma					0.1	0.1							
Neuronal tumors													
Medulloblastoma	0.0	0.1			0.1	0.1							
Neuroblastoma									0.1	0.0			
Meningeal tumors													
Granular cell tumor	0.1	0.0	0.2	0.0	0.2	0.0			0.2	0.1		0.2	0.0
Meningioma					0.1	0.1			0.1	0.0			
Meningeal sarcoma	0.1	0.0											
Epithelial tumors													
Ependymoma			0.1	0.0								0.2	0.0
Miscellaneous													
Malignant reticulosis	0.1	0.1											
Hemangioma									0.1	0.0			
Osteosarcoma	0.1	0.0										0.1	0.0
Sarcoma									0.1	0.0			

M and F represent male and female, respectively. Numbers in the table indicate incidences (%).

were higher in SD rats than in F344 rats and also in male SD rats than in female SD rats. The incidences of granular cell tumor showed a tendency to be higher in SD rats than in F344 rats and also in male SD rats than in female SD rats. There were no clear differences in the incidences of brain tumors among the previously reported HCD and the present HCD in both F344 and SD rats.

Discussion

In order to accurately assess the carcinogenicity of chemicals in the rat CNS, sufficient information concerning occurrence and biological features of spontaneous tumors is very important. The present study presents the data on the type, incidence and age at detection of CNS tumors in F344/DuCrlCrlj and Crl:CD(SD) rats collected from in-house background data-collection studies and control groups of carcinogenicity studies at our laboratory, together with those previously reported in F344 and SD rats[9–22].

In carcinogenicity studies, Peto's test[23, 24] is commonly employed as one of the tools of statistical analysis for evaluation of carcinogenicity of test chemicals. In this test, every type of tumor observed is categorized as either a common (incidence: more than 1%) or rare tumor (incidence: 1% or less) based on the HCD, and a statistical analysis of each tumor is done with different statistical decision rules based on whether the incidence of the tumor in HCD is more than 1% or not. Although CNS tumors are generally rare, the incidences of astrocytoma, oligodendroglioma, granular cell tumor and meningioma in SD rats were sometimes more than 1% in the present data and/or the previously reported HCD[16–18, 20–22]. Increased incidences of these tumors in carcinogenicity studies should be carefully evaluated from the viewpoints of statistical analysis, dose-response relationship, incidence range, age at tumor detection, survival period and so on.

It seems reasonable to consider that the type and incidence of rat CNS tumors may change with time[25]. However, there were no time-related changes detected in the present data obtained from F344/DuCrlCrlj and Crl:CD(SD) rats during around 15 years. In addition, the incidence of every tumor was similar, even though different vehicles and administration routes were employed. Moreover, there were little differences in the type and incidence of rat CNS tumors between the present and previously reported data. This suggests that CNS tumors are hardly influenced by circumstances in F344 and SD rats.

Although it is impossible to correctly determine the day of onset of CNS tumors, it is possible to presume which type of tumors occurs earlier or later based on the day of death or premature termination in a large cohort of rats. Among astrocytoma, oligodendroglioma and granular cell tumor, oligodendroglioma developed earliest and granular cell tumor latest in both F344/DuCrlCrlj and Crl:CD(SD) rats. This order is the same as that in Rcc Han:Wistar rats[26], and it seems to be common in F344, SD and Wistar rats.

Although it was difficult to detect sex and strain differences in the incidences of rare tumors in F344 and SD rats, the incidences of astrocytoma and granular cell tumors were higher than those of the other CNS tumors in SD rats. In ad-

Table 8. Cumulative Incidences of Spontaneous Brain Tumors in SD Rats

	Crj: SD (IGS)		Crl: SDBR		Crl: SDBR		Crl: SDBR		Crl: SDBR (IGS)		Crj: SD		Crj: SD (IGS)		Crl: SDBR (IGS)		Crl: SD		Crl: SDBR		Crl: SDBR		Hsd: SD	Hsd: SD	
	Present study		McMartin *et al.* 1992[15]		Charles River Lab. 1992[16]		Perry *et al.* 1999[17]		Perry *et al.* 1999[17]		Iwata *et al.* 1999[18]		Iwata *et al.* 1999[18]		Charles River Lab. 2001[19]		Charles River Lab. 2004[20]		Baldrick 2005[21]		Baldrick 2005[21]		Dinse *et al.* 2010[13]	NTP 2011[22]	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	F	M	F
Glial tumors																									
Astrocytoma	2.0	1.1	0.7	0.5	1.3	0.2	1.2	0.4	1.9	0.0	3.6	0.0	2.0	0.0	0.9	0.6	1.2	0.5	1.5	1.2	1.6	0.4	0.4	2.0	0.0
Oligodendroglioma	0.4	0.2	0.2	0.0											0.1	0.1	0.1	0.2					0.2		
Glioma			0.2	0.0	0.4	0.4									0.2	0.1	0.1	0.0					0.0		
Neuronal tumors																									
Medulloblastoma			0.2	0.0																					
Ganglioneuroma															0.0	0.1									
Neuroma																	0.1	0.0							
Meningeal tumors																									
Granular cell tumor	0.7	0.2	0.2	0.0	0.3	0.2	1.2	0.0	0.0	0.3					0.7	0.4	0.6	0.3	1.0	0.3	1.3	0.8			
Meningioma	0.1	0.0							0.6	0.0	0.0	0.9	0.0	2.0					1.7	0.6	1.3	0.6			
Meningeal sarcoma	0.1	0.0							0.3	0.0					0.1	0.1	0.1	0.0							
Epithelial tumors																									
Ependymoma									0.0	0.3					0.1	0.0	0.1	0.0							
Ependymoblastoma			0.2	0.0																					
Choroid plexus papilloma																	0.1	0.0							
Miscellaneous																									
Malignant reticulosis	0.1	0.0																							
Hemangioma	0.0	0.1																							
Hemangiosarcoma															0.1	0.0	0.1	0.0							
Osteosarcoma	0.1	0.0																							
Malignant pinealoma											0.0	0.9													

M and F represent male and female, respectively. Numbers in the table indicate incidences (%).

dition, the incidence of astrocytoma was almost consistently higher in SD rats than in F344 rats and also in males than in females, suggesting that the difference in the occurrence of astrocytoma may be related to rat strain and sex. A similar tendency was also sometimes observed in the incidence of granular cell tumor, although the tendency was not always consistent.

Krinke *et al*. described that meningioma was not observed in SD rats[27]. In addition, several researchers[15–17] reported that meningioma was never detected in HCD for SD (not-IGS) rats obtained from Charles River UK. On the other hand, its incidence was reported to be more than 1% by Iwata *et al*.[18] and Baldrick[21]. The data of Iwata *et al*.[18] were obtained from a small number of CD(SD)IGS rats (incidence: 2% (1/50) of females), while the data of Baldrick[21] were collected from 13 studies with a total of more than 460 male and 460 female rats of an SD (not-IGS) strain (Charles River UK) (incidences: 1.7% (8/470) and 1.3% (6/461) in each male group, and 0.6% (3/476) and 0.6% (3/468) in each female group). Thus, the relation between the occurrence of meningioma and rat sub-strain was not clear.

In conclusion, the present study clarified the following. (1) The incidences of all CNS tumors observed in F344/DuCrlCrlj rats were less than 1%. (2) The incidences of malignant astrocytoma and granular cell tumor were higher in males than in females in Crl:CD(SD) rats. (3) The incidences of astrocytoma and granular cell tumor were higher in Crl:CD(SD) rats than in F344/DuCrlCrlj rats. (4) Among astrocytoma, oligodendroglioma and granular cell tumor, oligodendroglioma was detected at the youngest age, followed by astrocytoma, and ultimately, granular cell tumor developed in both F344/DuCrlCrlj and Crl:CD(SD) rats. The incidences observed in our study were almost consistent with those previously reported in F344 and SD rats[9–22].

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