

neural	0
(central nervous system	
development	0)
cell migration	0
apoptosis	1
proliferation	0
cell adhesion	1
others	7
EST	7
<hr/>	
total	16

example

Bcl2-like 12

Fig. 43.

Ontology analysis of genes showing decreased expression in the white matter of rats at weaning exposed to decabromodiphenyl ether during the period from the mid-gestation to the end of lactation.

Up-regulated (≥ 2 -fold)

Down-regulated ($\geq 1/2$ -fold)

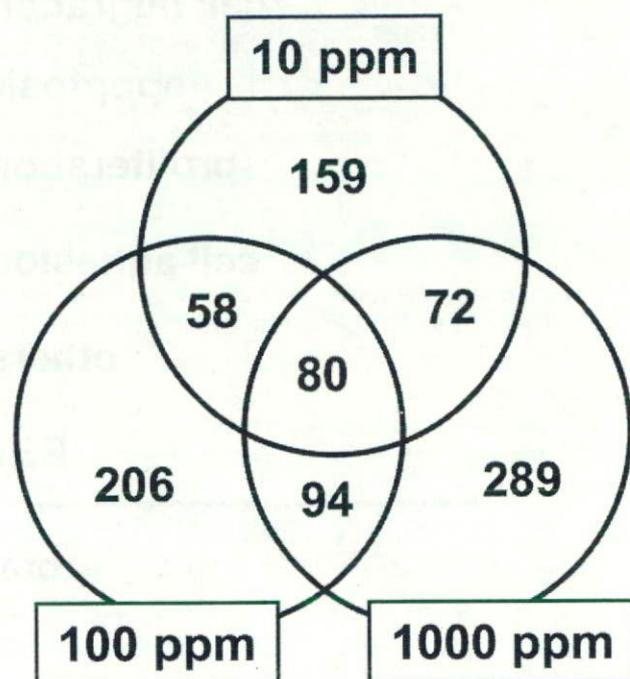
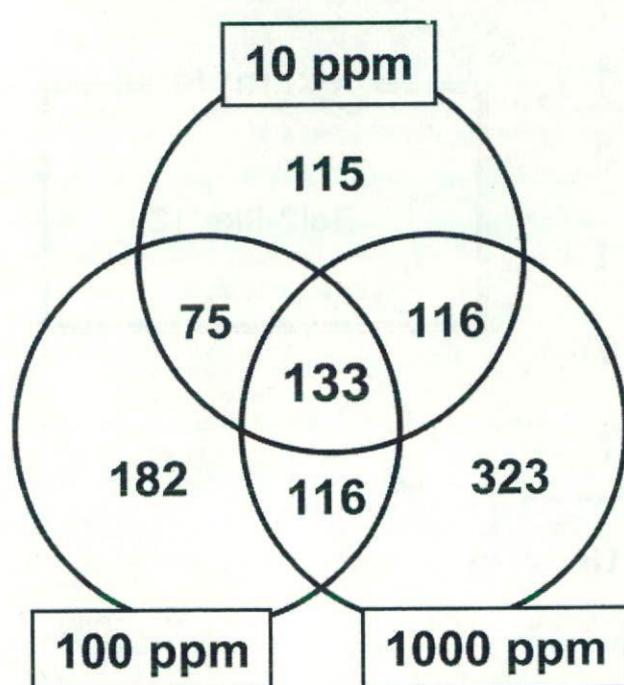


Fig. 44.

Venn diagram of genes showing altered expression in the hippocampal CA1 region of rats at weaning exposed to decabromodiphenyl ether during the period from the mid-gestation to the end of lactation.

neural	11
(central nervous system development)	8)
cell migration	3
apoptosis	3
proliferation	0
cell adhesion	3
others	53
EST	52
<hr/>	
total	133

example
Neuregulin 1
Forkhead box D1
Notch 1
Cholecystokinin
Granzyme G
Histone deacetylase 3

Fig. 45. Ontology analysis of genes showing increased expression in the hippocampal CA1 region of rats at weaning exposed to decabromodiphenyl ether during the period from the mid-gestation to the end of lactation.

neural	7	
(central nervous system development)	4)	
cell migration	1	
apoptosis	1	
proliferation	1	
cell adhesion	1	
others	26	
EST	43	
<hr/>		
total	80	

example
Nerve growth factor receptor
Reelin
Claudin 1
Zinc finger homeobox 1b
Thioredoxin-like 1

Fig. 46. Ontology analysis of genes showing decreased expression in the hippocampal CA1 region of rats at weaning exposed to decabromodiphenyl ether during the period from the mid-gestation to the end of lactation.

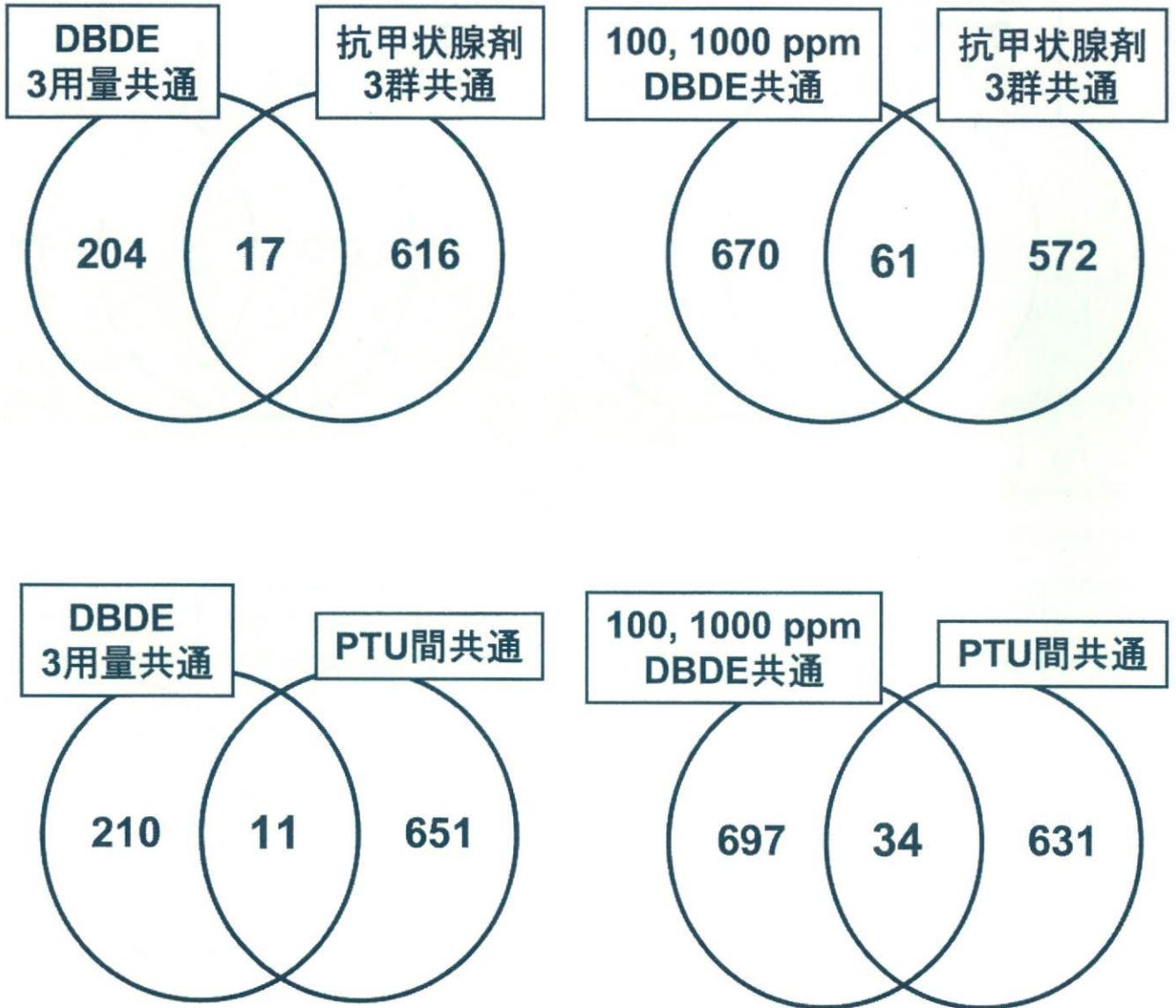


Fig. 47.

白質において抗甲状腺剤投与、DBDE投与に共通して発現増加した遺伝子数.

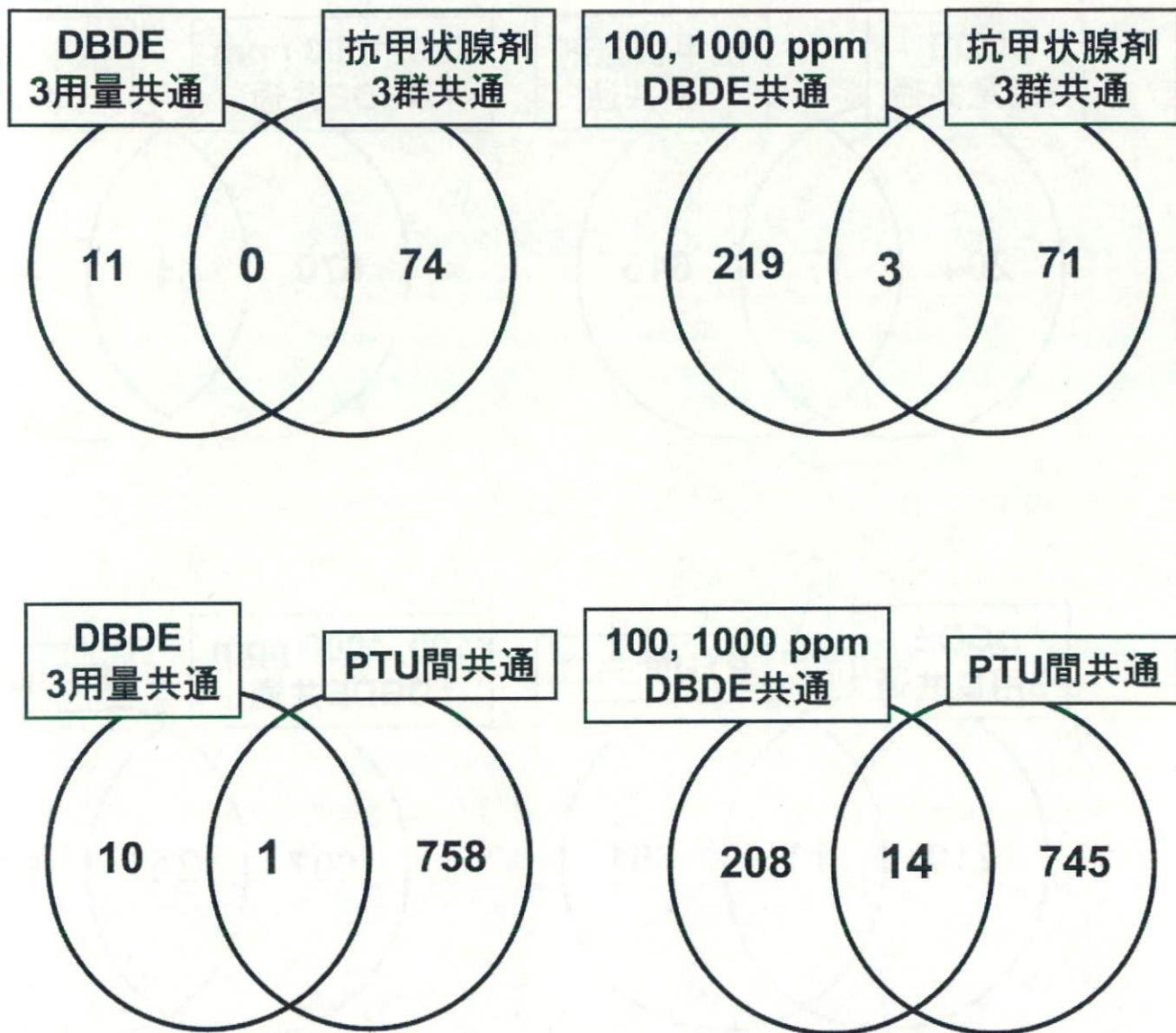


Fig. 48.

白質において抗甲状腺剤投与、DBDE投与に共通して発現減少した遺伝子数。

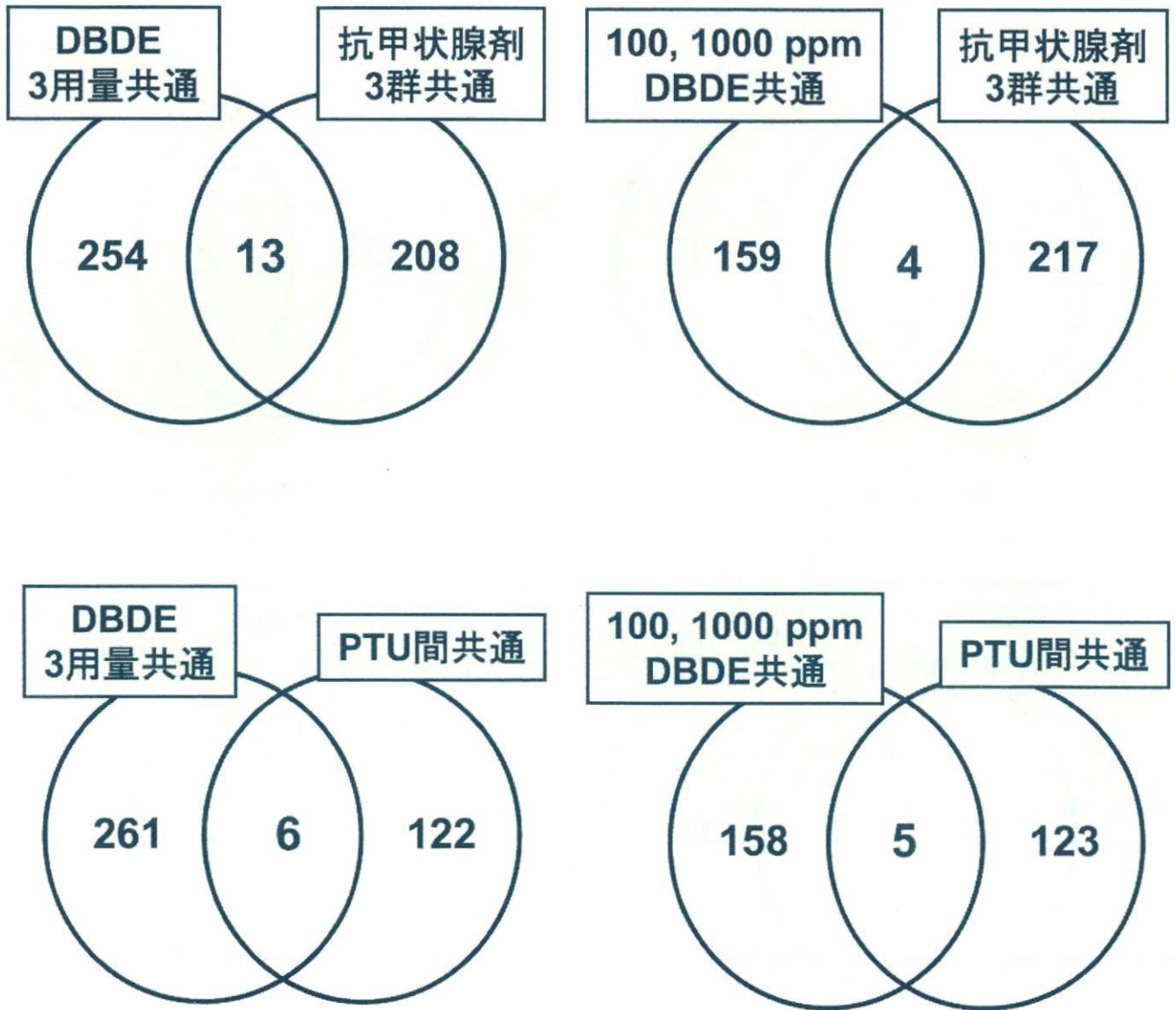


Fig. 49.

海馬CA1において抗甲状腺剤投与、DBDE投与に共通して発現増加した遺伝子数。

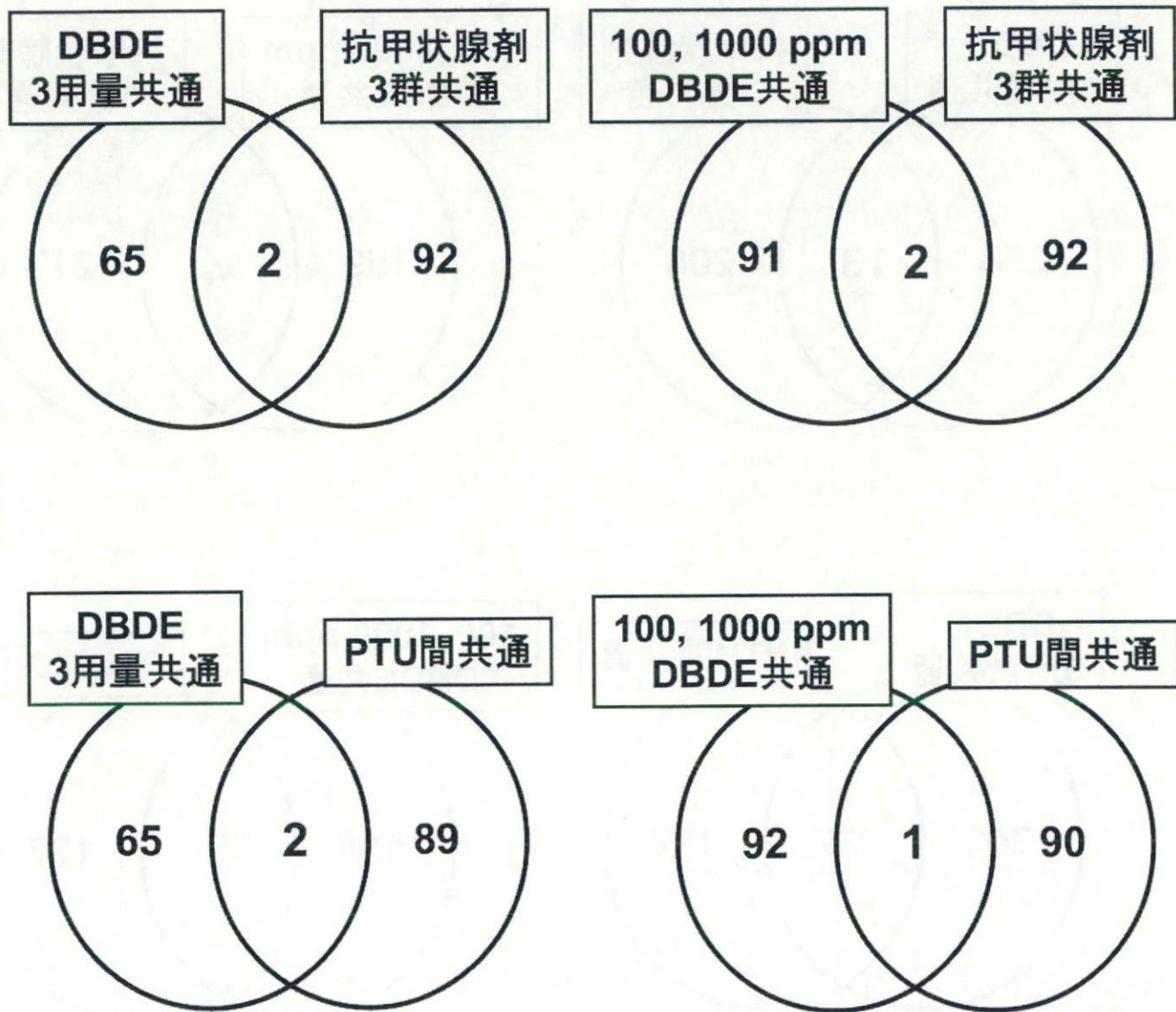
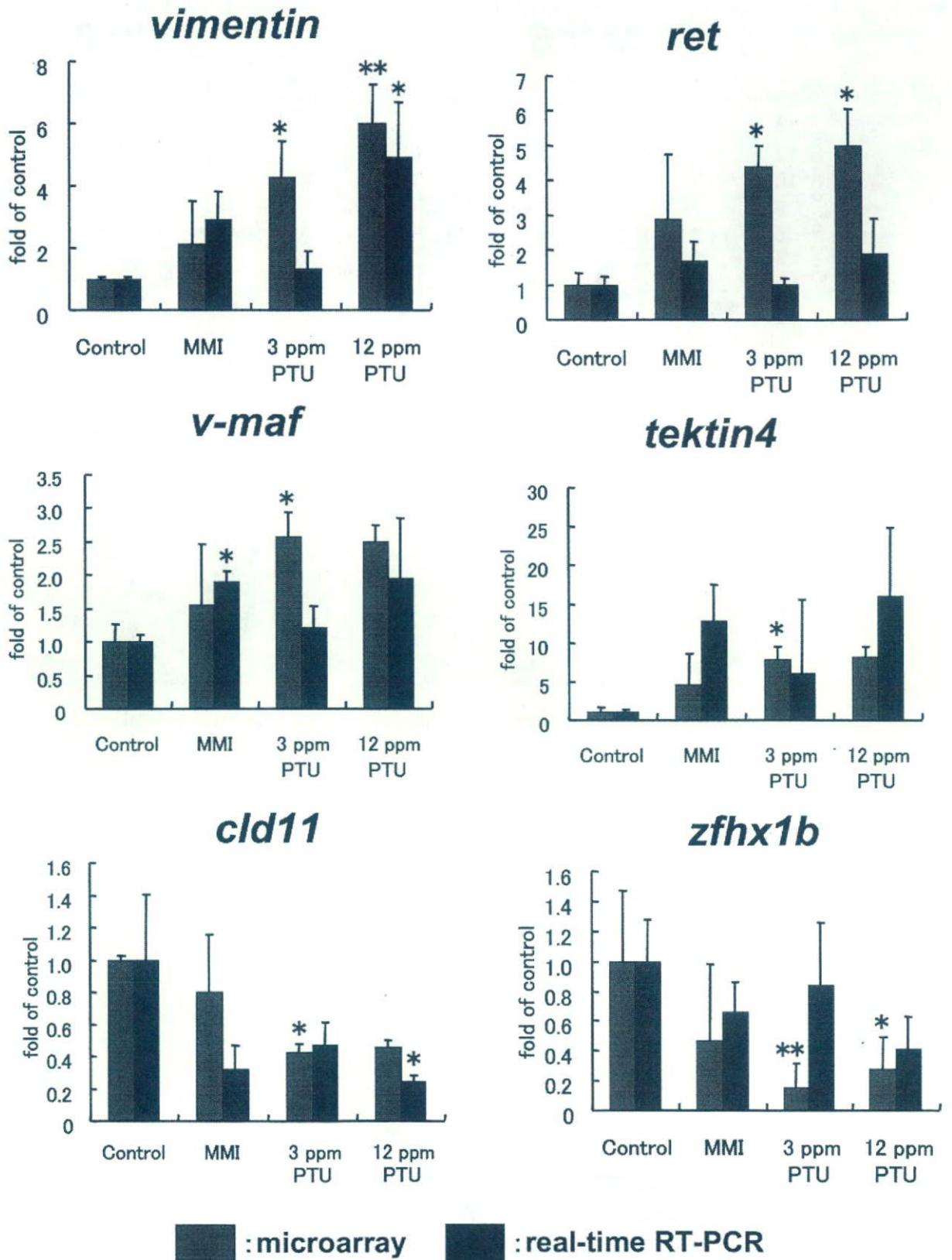
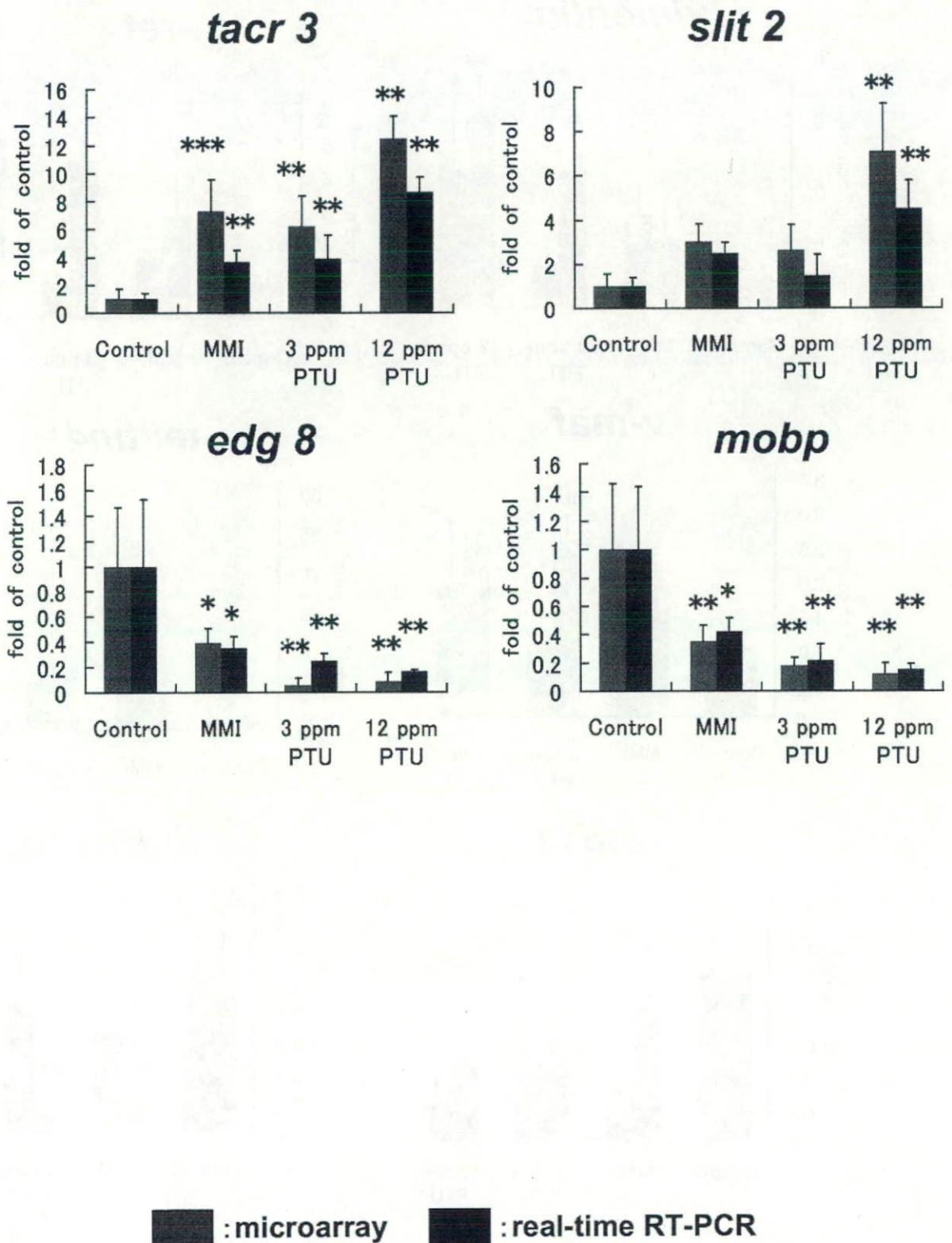


Fig. 50.
海馬CA1において抗甲状腺剤投与、DBDE投与に共通して発現減少した遺伝子数.



* : $p < 0.05$ vs. control, ** : $p < 0.01$ vs. control

Fig. 51.
Validation analysis of mRNA expression changes in the white matter of rat offspring exposed perinatally to anti-thyroid agents by real-time RT-PCR.



* : $p < 0.05$ vs. control, ** : $p < 0.01$ vs. control

Fig. 52.
Validation analysis of mRNA expression changes in the hippocampal CA1 region of rat offspring exposed perinatally to anti-thyroid agents by real-time RT-PCR.

Table 38.

Quantitative analysis of vimentin-, ret-, or GFAP-immunoreactive cells in the cerebral white matter of the offspring exposed to antithyroid agents during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	Control	MMI (ppm)		PTU (ppm)	
		200	3	12	12
No. of offspring examined	6	10	10	10	10
Vimentin (+) cell count (/mm ²)	6.2±3.8 ^a	149.1±32.7**	62.0±36.7	118.7±34.6**	118.7±34.6**
Ret (+) cell count (/mm ²)	15.3±2.1	48.7±13.4**	26.4±8.4	33.9±9.1*	33.9±9.1*
GFAP (+) cell count (/mm ²)	92.8±4.7	203.2±59.7**	126.1±17.4	152.5±19.7*	152.5±19.7*

^a Mean ± SD.

*** Significantly different from the control by Dunnett's test or Dunnett-type rank-sum test (**p*<0.05, ***p*<0.01).

Abbreviations: MMI, methimazole; PTU, propylthiouracil; PND, postnatal day; GFAP, glial fibrillary acidic protein.

Table 39.

Quantitative analysis of vimentin- or ret-immunoreactive cells in the cerebral white matter of the offspring exposed to decabromodiphenyl ether (DBDE) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	DBDE in diet (ppm)			
	0	10	100	1000
No. of offspring examined	5	5	5	5
Vimentin (+) cell count (/mm ²)	12.7±8.9 ^a	38.1±18.1	55.9±22.3**	85.3±18.5**
Ret (+) cell count (/mm ²)	6.6±2.5	20.1±2.2**	29.3±5.1**	34.2±5.3**

^a Mean ± SD.

** Significantly different from the 0 ppm control by Dunnett's test or Dunnett-type rank-sum test (*p*<0.01).

Abbreviations: DBDE, decabromodiphenyl ether; PND, postnatal day.

Table 40.

Quantitative analysis of vimentin-immunoreactive cells in the cerebral white matter of the offspring exposed to 1,2,5,6,9,10-hexabromocyclododecane (HBCD) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	HBCD in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
Vimentin (+) cell count (/mm ²)	20.9 ± 8.3 ^a	33.3 ± 10.2	54.9 ± 24.7**	40.0 ± 11.8**

^a Mean ± SD.

** Significantly different from the 0 ppm control by Dunnett's test or Dunnett-type rank-sum test ($p < 0.01$).

Abbreviations: HBCD, 1,2,5,6,9,10-hexabromocyclododecane; PND, postnatal day.

Table 41.

Quantitative analysis of vimentin-immunoreactive cells in the cerebral white matter of the offspring exposed to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	TBBPA in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	8	8	8	8
Vimentin (+) cell count (/mm ²)	15.1 ± 5.1 ^a	19.0 ± 5.8	19.6 ± 4.7	21.0 ± 8.6

^a Mean ± SD.

Abbreviations: TBBPA, tetrabromobisphenol A; PND, postnatal day.

Table 42.

Immunoexpression intensity of candidate molecules selected from microarray profiling in the white matter of the offspring exposed to antithyroid agents during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	Control	MMI (ppm)		PTU (ppm)	
		200	3	12	
No. of offspring examined	6	10	9	9	
DCC	1.7 ± 0.5 ^a	3.0 ± 0.8**	2.1 ± 0.6	3.0 ± 0.7**	
Cld11	1.5 ± 0.5	3.1 ± 0.6**	1.7 ± 0.8	2.3 ± 0.9	

^a Intensity scores of immunoreactivity: 0, none; 1, minimal; 2, slight; 3, moderate; and 4, prominent. Values were expressed as mean ± SD.

** Significantly different from the control by Mann-Whitney's *U*-test ($p < 0.01$).

Abbreviations: MMI, methimazole; PTU, propylthiouracil; PND, postnatal day; DCC, deleted in colorectal cancer protein.

Table 43.

Immunoexpression intensity of candidate molecules selected from microarray profiling in the white matter of the offspring exposed to decabromodiphenyl ether (DBDE) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	DBDE in diet (ppm)			
	0	10	100	1000
No. of offspring examined	5	5	5	5
Cld11	2.4 ± 0.5	1.4 ± 0.5*	1.6 ± 0.5	1.6 ± 0.5
Heregulin	1.6 ± 0.5	2.0 ± 0.7	2.4 ± 0.9	3.0 ± 0.7*
Crk	1.4 ± 0.9	2.2 ± 0.4	2.4 ± 1.1	3.4 ± 0.5**
Smad1/2/3	2.8 ± 0.4	2.4 ± 0.5	2.0 ± 1.0	1.4 ± 0.5*

^a Intensity scores of immunoreactivity: 0, none; 1, minimal; 2, slight; 3, moderate; and 4, prominent. Values were expressed as mean ± SD.

*** Significantly different from the 0 ppm control by Mann-Whitney's *U*-test (**p* < 0.05, ***p* < 0.01).

Abbreviations: DBDE, decabromodiphenyl ether; PND, postnatal day.

Table 44.

Quantitative analysis of reelin-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to antithyroid agents during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	Control	MMI (ppm)	PTU (ppm)
		200	12
No. of offspring examined	6	5	9
Reelin (+) cell count (/mm ²)	38.8 ± 14.2 ^a	73.8 ± 16.7*	70.4 ± 26.3*

^a Mean ± SD.

* Significantly different from the control by Dunnett's test (*p* < 0.05).

Abbreviations: MMI, methimazole; PTU, propylthiouracil; PND, postnatal day.

Table 45.

Quantitative analysis of reelin-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to decabromodiphenyl ether (DBDE) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	DBDE in diet (ppm)			
	0	10	100	1000
No. of offspring examined	6	5	5	5
Reelin (+) cell count (/mm ²)	38.8 ± 14.2 ^a	46.1 ± 7.2	56.4 ± 13.5	68.3 ± 15.3*

^a Mean ± SD.

* Significantly different from the control by Dunnett's test (*p* < 0.05).

Abbreviations: DBDE, decabromodiphenyl ether; PND, postnatal day.

Table 46.

Quantitative analysis of reelin-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to 1,2,5,6,9,10-hexabromocyclododecane (HBCD) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	HBCD in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
Reelin (+) cell count (/mm ²)	84.4 ± 26.6 ^a	97.5 ± 26.6	130.3 ± 37.8**	102.5 ± 15.7

^a Mean ± SD.

** Significantly different from the control by Dunnett's test ($p < 0.01$).

Abbreviations: HBCD, 1,2,5,6,9,10-hexabromocyclododecane; PND, postnatal day.

Table 47.

Quantitative analysis of reelin-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	TBBPA in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	8	8	7	7
Reelin (+) cell count (/mm ²)	98.5 ± 18.1 ^a	120.9 ± 19.6	144.8 ± 24.3**	143.4 ± 32.2**

^a Mean ± SD.

** Significantly different from the controls by Dunnett's test ($p < 0.01$).

Abbreviations: TBBPA, tetrabromobisphenol A; PND, postnatal day.

Table 48.

Quantitative analysis of NeuN-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to antithyroid agents during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	Control	MMI (ppm)		PTU (ppm)	
		200	3	12	
No. of offspring examined	10	10	10	6	
NeuN (+) cell count (/mm ²)	73.7 ± 17.4 ^a	174.0 ± 29.8**	104.7 ± 13.6**	126.2 ± 13.0**	

^a Mean ± SD.

** Significantly different from the control by Dunnett's test ($p < 0.01$).

Abbreviations: MMI, methimazole; PTU, propylthiouracil; PND, postnatal day.

Table 49.

Quantitative analysis of NeuN-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to decabromodiphenyl ether (DBDE) during the period from the mid-gestation to the end of lactation. Analysis at PNW 11.

	DBDE in diet (ppm)			
	0	10	100	1000
No. of offspring examined	10	10	10	9
NeuN (+) cell count (/mm ²)	62.7 ± 9.3 ^a	74.6 ± 17.0	68.3 ± 17.5	87.0 ± 16.4**

^a Mean ± SD.

** Significantly different from the control by Dunnett's test ($p < 0.01$).

Abbreviations: DBDE, decabromodiphenyl ether; PND, postnatal day.

Table 50.

Quantitative analysis of NeuN-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to 1,2,5,6,9,10-hexabromocyclododecane (HBCD) during the period from the mid-gestation to the end of lactation. Analysis at PNW 11.

	HBCD in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
NeuN (+) cell count (/mm ²)	71.1 ± 16.6 ^a	88.0 ± 24.8	93.8 ± 21.4	104.3 ± 17.6**

^a Mean ± SD.

** Significantly different from the 0 ppm control by Dunnett's test ($p < 0.01$).

Abbreviations: HBCD, 1,2,5,6,9,10-hexabromocyclododecane; PND, postnatal day.

Table 51.

Quantitative analysis of NeuN-immunoreactive cells outside of the granule cell layer in the hippocampal dentate gyrus of the offspring exposed to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation. Analysis at PNW 11.

	TBBPA in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
NeuN (+) cell count (/mm ²)	58.0 ± 13.7 ^a	64.6 ± 14.0	74.7 ± 11.9*	82.3 ± 16.1**

^a Mean ± SD.

* ** Significantly different from the 0 ppm control by Dunnett's test (* $p < 0.05$, ** $p < 0.01$).

Abbreviations: TBBPA, tetrabromobisphenol A; PND, postnatal day.

Table 52.

Quantitative analysis of Ephrin A5-immunoreactive cells in the hippocampal CA1 region of the offspring exposed to antithyroid agents during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	Control	MMI (ppm)		PTU (ppm)	
		200	3	12	
No. of offspring examined	6	6	8	9	
Ephrin A5 (+) cell count (/mm ²)	4.7 ± 2.3 ^a	9.1 ± 6.6	16.3 ± 5.2**	17.5 ± 7.1**	

^a Mean ± SD.

** Significantly different from the control by Dunnett's test ($p < 0.01$).

Abbreviations: MMI, methimazole; PTU, propylthiouracil; PND, postnatal day.

Table 53.

Quantitative analysis of Ephrin A5-immunoreactive cells in the hippocampal CA1 region of the offspring exposed to decabromodiphenyl ether (DBDE) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	DBDE in diet (ppm)			
	0	10	100	1000
No. of offspring examined	6	5	5	5
Ephrin A5 (+) cell count (/mm ²)	3.7 ± 2.8 ^a	2.8 ± 2.6	4.7 ± 2.1	8.2 ± 2.3

^a Mean ± SD.

Abbreviations: DBDE, decabromodiphenyl ether; PND, postnatal day.

Table 54.

Quantitative analysis of Ephrin A5-immunoreactive cells in the hippocampal CA1 region of the offspring exposed to 1,2,5,6,9,10-hexabromocyclododecane (HBCD) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	HBCD in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
Ephrin A5 (+) cell count (/mm ²)	2.5 ± 3.3 ^a	3.1 ± 3.5	4.8 ± 3.5	3.6 ± 3.4

^a Mean ± SD.

Abbreviations: HBCD, 1,2,5,6,9,10-hexabromocyclododecane; PND, postnatal day.

Table 55.

Quantitative analysis of Ephrin A5-immunoreactive cells in the hippocampal CA1 region of the offspring exposed to tetrabromobisphenol A (TBBPA) during the period from the mid-gestation to the end of lactation. Analysis at PND 21.

	TBBPA in diet (ppm)			
	0	100	1000	10,000
No. of offspring examined	10	10	10	10
Ephrin A5 (+) cell count (/mm ²)	3.7 ± 7.2 ^a	12.2 ± 15.5	8.6 ± 9.8	9.8 ± 11.9

^a Mean ± SD.

Abbreviations: TBBPA, tetrabromobisphenol A; PND, postnatal day.

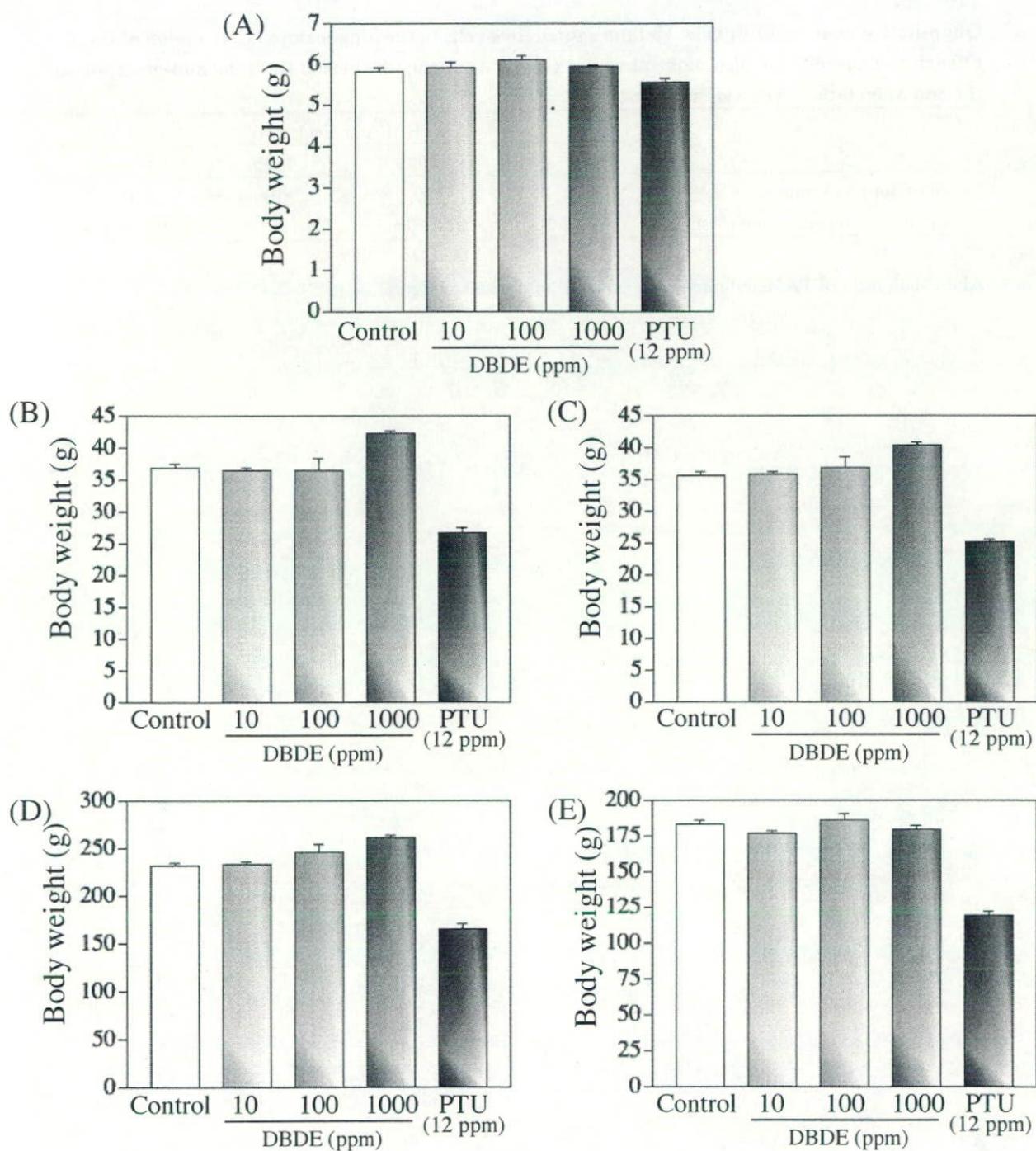


Fig. 53.

Decabromodiphenyl ether (DBDE) および propylthiouracil (PTU) の胎児期および授乳期慢性曝露による一般成長に及ぼす影響。DBDE および PTU の胎児期および授乳期慢性曝露による一般成長に及ぼす影響を、出生時 (A)、離乳時 (3 週齢; B; 雄; C; 雌) および行動実験開始時 (7 週齢; D; 雄; E; 雌) の体重を指標として検討した。その結果、離乳時 (3 週齢) および行動実験開始時 (7 週齢) において、雌雄共に PTU 慢性曝露による著明な体重減少が認められた。一方、DBDE 慢性曝露ラットでは、むしろ体重の増加傾向が認められた。

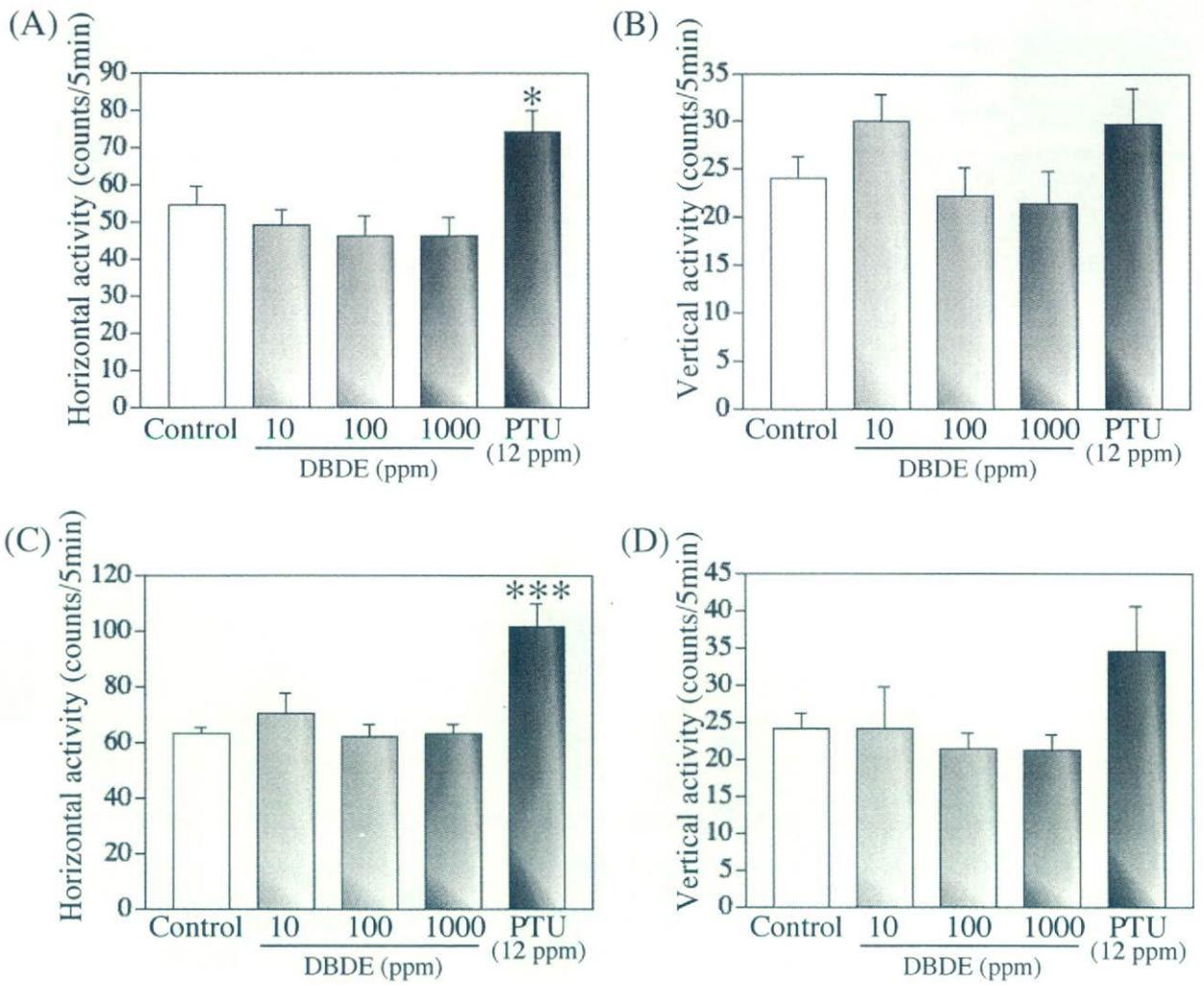


Fig. 54.

DBDE および PTU の胎児期および授乳期慢性曝露による自発運動量に及ぼす影響。 一般行動観察の結果、PTU の慢性曝露により雄 (A, B)、雌 (C, D) 共に著しい自発運動量の増加が認められた。一方、DBDEの慢性曝露では自発運動量に影響を及ぼさなかった。 * $p < 0.05$, *** $p < 0.001$ vs. control group

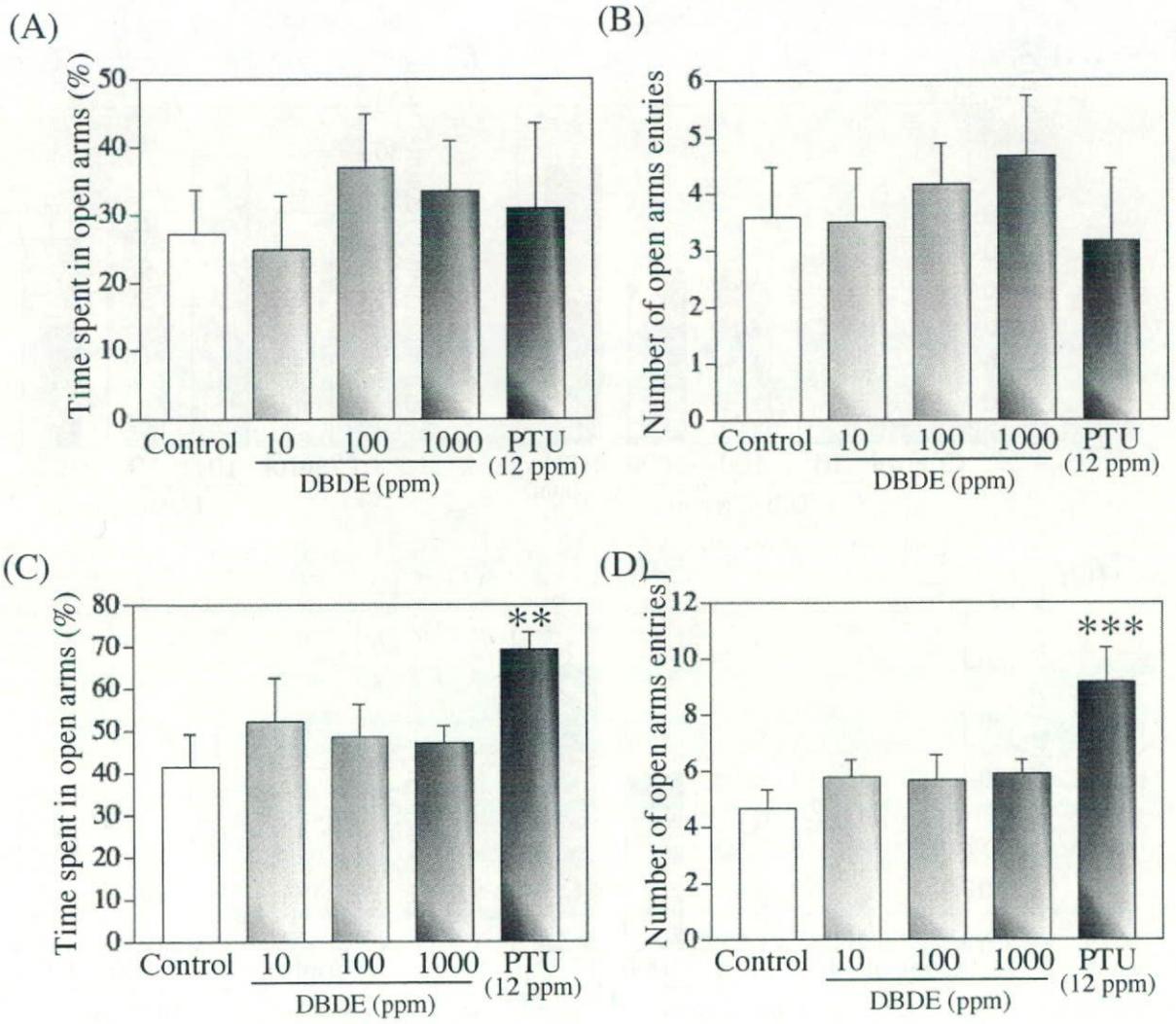


Fig. 55.

DBDE および PTU の胎児期および授乳期慢性曝露による不安感受性に及ぼす影響。高架式十字迷路法に従い PTU および DBDE 慢性曝露による不安感受性の変化について検討したところ、雄 (A, B) ではいずれの化学物質曝露でも有意な変化は認められなかった。一方、雌 (C, D) では、PTU 慢性曝露においてのみ、open arms 滞在時間の割合および侵入回数の有意な増加が認められた。 ** $p < 0.01$, *** $p < 0.001$ vs. control group