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APPENDIX

Table i Body weight (BW), daily weight gain (DWG), daily food intake (DFI), uterine weight (UW), and percentage of uterine-to-body weight ratio (% UW/BW) of estrogen treated ovariectomized (Ovx+E_2) rats.

No	BW (g)	DWG (g/day)	DFI (g/day)	UW (g)	% UW/BW
1	232.5	0.93	12.46	0.395	0.170
2	232.5	0.79	12.49	0.405	0.174
3	230.0	0.93	12.68	0.358	0.156
4	237.5	1.20	12.96	0.371	0.156
5	235.0	0.93	12.96	0.339	0.144
6	247.5	2.04	12.95	0.267	0.108
7	240.0	1.48	13.56	0.299	0.125
8	242.5	1.67	13.65	0.355	0.146
9	245.0	1.48	12.35	0.357	0.146
10	257.5	1.57	13.10	0.390	0.151
11	237.5	1.48	13.10	0.338	0.142
12	225.0	0.89	12.32	0.314	0.140
13	212.5	0.63	12.32	0.316	0.149
14	212.5	0.45	12.39	0.331	0.156
15	220.0	0.89	12.39	0.394	0.181
16	242.5	1.34	12.59	0.480	0.194
17	257.5	1.61	13.21	0.380	0.148
18	250.0	1.39	13.40	0.310	0.124
19	225.0	1.11	12.95	0.370	0.164
20	245.0	1.76	13.56	0.305	0.124
21	245.0	1.39	13.65	0.393	0.160
22	232.5	1.67	12.34	0.365	0.157
23	240.0	1.30	12.34	0.317	0.132
24	232.5	0.89	12.59	0.368	0.158
25	232.5	1.07	13.89	0.396	0.172
26	247.5	1.34	13.89	0.390	0.158
27	215.0	0.71	13.21	0.411	0.189
28	252.5	1.19	13.15	0.418	0.166
29	265.0	1.38	13.21	0.418	0.156
30	240.0	1.25	13.21	0.381	0.159
31	237.5	1.00	11.84	0.346	0.146
32	225.0	0.63	11.84	0.374	0.161
33	225.0	0.69	12.76	0.347	0.151
34	250.0	1.13	12.76	0.378	0.154
35	265.0	1.25	14.02	0.377	0.142
36	257.5	1.38	14.02	0.327	0.126
Mean	238.61	1.19	12.95	0.363	0.152
SEM	2.27	0.06	0.10	0.007	0.003

Table ii Body weight (BW), daily weight gain (DWG), daily food intake (DFI), uterine weight (UW), and percentage of uterine-to-body weight ratio (% UW/BW) of ovariectomized (Ovx) rats.

No	BW (g)	DWG (g/day)	DFI (g/day)	UW (g)	% UW/BW
1	280.0	2.21	13.26	0.129	0.046
2	297.5	3.33	15.02	0.114	0.038
3	280.0	3.06	15.63	0.135	0.048
4	285.0	2.87	15.79	0.124	0.044
5	300.0	3.70	15.69	0.118	0.039
6	270.0	2.96	14.86	0.107	0.040
7	285.0	3.15	16.03	0.116	0.041
8	307.5	3.61	16.43	0.110	0.036
9	272.5	3.06	15.47	0.094	0.034
10	270.0	3.06	15.14	0.098	0.036
11	297.5	3.80	15.14	0.113	0.038
12	262.5	2.05	15.23	0.123	0.047
13	270.0	2.41	15.23	0.125	0.045
14	275.0	2.77	14.34	0.135	0.049
15	250.0	2.32	14.34	0.102	0.041
16	310.0	3.75	17.54	0.146	0.047
17	300.0	3.21	17.54	0.132	0.044
18	300.0	3.30	16.36	0.119	0.039
19	277.5	2.95	16.36	0.104	0.037
20	295.0	2.69	14.86	0.092	0.031
21	280.0	3.15	14.40	0.106	0.038
22	282.5	2.87	16.03	0.109	0.039
23	282.5	3.15	16.43	0.105	0.037
24	282.5	2.50	15.32	0.151	0.053
25	277.5	2.68	15.25	0.116	0.042
26	282.5	2.50	16.30	0.120	0.042
27	305.0	3.13	16.30	0.141	0.045
28	260.0	2.41	15.51	0.131	0.051
29	292.5	2.86	15.51	0.126	0.043
30	292.5	2.38	14.47	0.094	0.032
31	275.0	2.25	14.47	0.116	0.042
32	297.5	2.56	14.29	0.118	0.039
33	285.0	1.88	14.29	0.133	0.047
34	297.5	2.44	14.94	0.106	0.035
35	287.5	2.25	14.94	0.121	0.041
36	272.5	1.94	13.17	0.111	0.040
37	267.5	1.81	15.30	0.116	0.043
38	320.0	2.56	15.30	0.114	0.035
Mean	284.87	2.78	15.33	0.118	0.041
SEM	2.44	0.08	0.16	0.002	0.001

Table iii Body weight (BW), daily weight gain (DWG), daily food intake (DFI), uterine weight (UW), and percentage of uterine-to-body weight ratio (% UW/BW) of proestrous (Pro) rats.

No	BW (g)	DWG (g/day)	DFI (g/day)	UW (g)	% UW/BW
1	227.5	0.76	11.86	0.788	0.346
2	210.0	0.69	11.86	0.407	0.194
3	232.5	1.20	12.87	0.627	0.270
4	250.0	1.67	13.74	0.677	0.271
5	235.0	1.20	13.74	0.684	0.291
6	250.0	1.67	13.43	0.544	0.218
7	237.5	1.57	13.32	0.812	0.342
8	262.5	2.31	14.99	0.649	0.247
9	270.0	1.67	13.15	0.781	0.289
10	237.5	1.30	12.66	0.766	0.323
11	227.5	1.30	12.92	1.047	0.460
12	225.0	0.98	11.31	0.656	0.288
13	207.5	0.71	11.31	0.436	0.200
14	230.0	1.07	11.55	0.683	0.294
15	225.0	1.07	11.55	1.057	0.470
16	250.0	1.61	13.03	0.991	0.392
17	235.0	1.16	12.97	0.744	0.310
18	255.0	1.79	14.08	0.481	0.189
19	227.5	1.25	13.71	0.412	0.179
20	240.0	1.94	13.43	0.622	0.259
21	237.5	1.67	13.15	0.776	0.327
22	227.5	1.30	12.66	0.548	0.241
23	237.5	1.76	12.92	0.549	0.231
24	237.5	1.16	12.06	0.501	0.211
25	240.0	1.25	13.03	0.452	0.188
26	245.0	1.52	14.08	0.389	0.157
27	260.0	1.79	13.71	0.705	0.264
28	262.5	1.38	13.61	0.436	0.171
29	265.0	1.31	13.61	0.743	0.275
30	255.0	1.25	11.85	0.715	0.280
31	230.0	1.00	11.85	0.515	0.224
32	242.5	1.31	13.53	0.562	0.229
33	290.0	1.63	14.57	0.405	0.141
34	282.5	1.75	14.57	0.360	0.126
35	247.5	1.38	13.79	0.625	0.253
36	275.0	1.63	13.79	0.659	0.237
Mean	243.61	1.39	13.06	0.633	0.261
SEM	3.11	0.06	0.16	0.030	0.013

Table iv Baseline, avoidance 1, and 2 latency times in seconds of inhibitory avoidance task and escape latency times in seconds of one-way escape task in the elevated T-maze of estrogen treated ovariectomized (Ovx+E_2), ovariectomized (Ovx), and proestrous (Pro) rats.

Ovx+E_2	Baseline	Avoidance 1	Avoidance 2	Escape
1	6.18	7.34	154.00	12.12
2	14.75	29.71	41.90	19.75
3	20.69	69.18	71.25	14.79
4	33.71	137.25	136.19	20.87
5	14.56	70.78	62.40	11.59
6	5.56	16.34	45.72	6.63
7	4.84	4.94	61.50	23.97
8	15.41	7.71	104.94	4.75
9	5.40	28.09	57.75	4.56
10	17.93	76.44	14.91	14.38
11	48.63	139.06	14.38	21.03
Mean	17.06	53.35	69.54	14.04
SEM	4.09	14.95	13.63	2.06

Ovx	Baseline	Avoidance 1	Avoidance 2	Escape
1	49.84	25.31	255.72	13.47
2	15.88	41.28	289.28	6.44
3	7.87	159.13	80.18	9.85
4	14.63	30.96	176.00	14.90
5	21.16	272.13	105.99	23.54
6	7.63	88.16	67.13	4.41
7	61.06	300.00	256.69	10.00
8	36.88	74.68	105.09	13.38
9	8.78	83.43	40.91	14.16
10	5.03	12.75	141.91	5.87
11	16.82	140.87	177.90	10.69
Mean	22.33	111.70	154.25	11.52
SEM	5.65	29.50	25.38	1.61

Pro	Baseline	Avoidance 1	Avoidance 2	Escape
1	8.22	61.72	300.00	13.46
2	92.22	204.37	14.91	32.16
3	20.40	8.69	162.56	15.47
4	13.69	6.87	50.85	28.84
5	22.15	78.21	300.00	25.00
6	10.78	12.38	196.34	16.12
7	9.81	284.44	32.57	6.69
8	12.12	207.50	297.15	21.65
9	54.59	137.19	148.22	37.91
10	30.56	91.19	219.12	24.63
11	12.68	6.41	11.12	23.78
Mean	26.11	99.91	157.53	22.34
SEM	7.75	29.13	34.94	2.71

Table v Total numbers of crosses, number of first 30 seconds crosses, time in outer zone, and time in inner zone of open field test of estrogen treated ovariectomized (Ovx+E_2), ovariectomized (Ovx), and proestrous (Pro) rats.

Ovx+E_2	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	115	22	137.81	162.19
2	99	23	175.77	124.23
3	93	17	168.77	131.23
4	90	16	36.00	264.00
5	87	23	97.02	202.98
6	139	30	215.23	84.77
7	107	18	224.04	75.96
8	111	23	216.55	83.45
9	79	19	111.40	188.60
10	102	15	174.38	125.62
11	148	20	213.03	86.97
Mean	106.36	20.55	160.91	139.09
SEM	6.42	1.29	18.06	18.06

Ovx	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	91	13	251.59	48.41
2	93	23	267.74	32.26
3	86	23	223.95	76.05
4	95	22	215.33	84.67
5	87	18	268.71	31.29
6	100	20	245.41	54.59
7	130	19	213.43	86.57
8	127	21	227.18	72.82
9	67	21	153.79	146.21
10	84	18	168.84	131.16
11	127	20	214.88	85.12
Mean	98.82	19.82	222.80	77.20
SEM	6.18	0.86	11.02	11.02

Pro	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	66	23	265.08	34.92
2	93	17	119.43	180.57
3	93	20	90.83	209.17
4	97	19	189.51	110.49
5	99	24	243.62	56.38
6	100	18	254.03	45.97
7	68	18	177.55	122.45
8	97	19	295.12	4.88
9	131	20	248.81	51.19
10	53	19	289.24	10.76
11	147	16	265.79	34.21
Mean	94.91	19.36	221.73	78.27
SEM	8.20	0.72	20.58	20.58

Table vi Serotonin (5-HT) contents, 5-HIAA contents, and ratio of 5-HIAA/5-HT of estrogen treated ovariectomized (Ovx+E_2) rats in frontal cortex, amygdala, hippocampus, nucleus accumbens, and septum.

5-HT	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	0.64	3.10	2.87	4.63	2.97
2	1.46	3.76	1.90	5.12	7.04
3	2.81	5.88	3.86	2.39	4.13
4	1.90	4.35	4.74	9.96	5.93
5	4.17	9.12	9.34	9.60	6.33
6	4.45	8.59	5.01	19.47	6.72
7	2.20	5.03	3.20	4.39	3.56
8	4.45	6.81	1.62	14.21	2.31
Mean	2.76	5.83	4.07	8.72	4.87
SEM	0.52	0.78	0.87	2.05	0.65

5-HIAA	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	3.20	9.54	16.98	14.74	10.97
2	6.94	10.87	9.62	13.19	11.67
3	5.85	9.98	7.34	14.96	8.24
4	7.34	9.90	16.34	20.86	13.59
5	9.36	17.18	20.11	22.63	16.23
6	8.88	9.40	14.72	25.14	11.98
7	7.44	14.10	17.91	19.97	10.61
8	7.59	11.24	8.32	28.29	8.52
Mean	7.08	11.53	13.92	19.97	11.48
SEM	0.67	0.97	1.71	1.90	0.92

5-HIAA/5-HT	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	4.99	3.08	5.92	3.19	3.69
2	4.74	2.89	5.07	2.58	1.66
3	2.08	1.70	1.90	6.25	1.99
4	3.86	2.27	3.45	2.09	2.29
5	2.25	1.88	2.15	2.36	2.56
6	1.99	1.09	2.94	1.29	1.78
7	3.38	2.80	5.60	4.55	2.98
8	1.71	1.65	5.14	1.99	3.69
Mean	3.12	2.17	4.02	3.04	2.58
SEM	0.46	0.25	0.57	0.57	0.28

Table vii Serotonin (5-HT) contents, 5-HIAA contents, and ratio of 5-HIAA/5-HT of ovariectomized (Ovx) rats in frontal cortex, amygdala, hippocampus, nucleus accumbens, and septum.

5-HT	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	1.72	9.11	6.63	11.06	11.41
2	6.16	14.40	12.01	18.77	13.95
3	2.25	5.33	5.29	11.71	7.70
4	1.67	5.75	4.47	10.18	4.89
5	1.98	4.69	3.04	8.06	4.71
6	3.57	8.11	7.31	15.62	3.08
7	6.76	15.21	15.38	13.93	23.06
8	7.27	6.82	5.29	17.86	5.58
9	3.25	7.61	5.77	6.15	3.35
10	4.53	7.32	4.17	10.87	11.06
Mean	3.92	8.43	6.94	12.42	8.88
SEM	0.68	1.14	1.22	1.29	1.97

5-HIAA	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	7.60	14.18	19.94	18.92	18.06
2	11.35	14.02	16.05	19.20	16.12
3	7.30	13.44	14.89	16.71	15.87
4	6.75	12.44	12.44	16.70	11.26
5	7.06	9.41	11.00	16.87	9.99
6	8.16	14.02	23.23	27.09	11.81
7	14.45	16.55	21.59	20.32	20.62
8	11.07	13.93	12.30	21.77	16.07
9	11.61	21.17	17.07	19.88	12.65
10	8.99	12.13	15.46	18.98	17.04
Mean	9.43	14.13	16.40	19.64	14.95
SEM	0.81	0.97	1.30	0.98	1.07

5-HIAA/5-HT	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	4.42	1.56	3.01	1.71	1.58
2	1.84	0.97	1.34	1.02	1.16
3	3.24	2.52	2.82	1.43	2.06
4	4.04	2.16	2.78	1.64	2.30
5	3.57	2.01	3.62	2.09	2.12
6	2.29	1.73	3.18	1.73	3.83
7	2.14	1.09	1.40	1.46	0.89
8	1.52	2.04	2.32	1.22	2.88
9	3.57	2.78	2.96	3.23	3.77
10	1.98	1.66	3.71	1.75	1.54
Mean	2.86	1.85	2.71	1.73	2.21
SEM	0.32	0.18	0.26	0.19	0.32

Table viii Serotonin (5-HT) contents, 5-HIAA contents, and ratio of 5-HIAA/5-HT of proestrous (Pro) rats in frontal cortex, amygdala, hippocampus, nucleus accumbens, and septum.

5-HT	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	8.38	13.15	6.17	9.92	16.84
2	2.97	17.69	17.24	4.52	5.75
3	2.39	6.01	5.53	9.24	7.26
4	2.61	5.27	26.99	14.41	5.11
5	2.60	4.96	4.60	8.08	11.27
6	3.94	5.43	5.32	16.24	5.95
7	3.29	7.52	6.49	14.46	9.25
8	4.81	7.64	2.80	16.96	6.92
9	4.84	6.88	4.81	7.79	3.85
10	4.57	6.11	4.19	6.75	8.30
Mean	4.04	8.07	8.41	10.84	8.05
SEM	0.57	1.30	2.42	1.37	1.19

5-HIAA	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	24.68	27.43	20.76	19.26	33.69
2	9.79	36.59	39.20	11.30	14.92
3	7.63	8.48	13.60	14.19	12.61
4	5.09	8.12	15.30	18.87	10.84
5	7.83	12.06	9.85	21.71	24.42
6	7.90	9.81	13.26	28.12	11.00
7	8.65	16.12	16.85	25.19	17.85
8	9.70	11.13	12.13	17.55	14.83
9	11.99	14.06	16.38	17.61	14.89
10	8.55	9.68	14.37	15.56	13.66
Mean	10.18	15.35	17.17	18.94	16.87
SEM	1.71	2.96	2.62	1.59	2.24

5-HIAA/5-HT	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	2.95	2.09	3.37	1.94	2.00
2	3.30	2.07	2.27	2.50	2.60
3	3.20	1.41	2.46	1.54	1.74
4	1.95	1.54	0.57	1.31	2.12
5	3.02	2.43	2.14	2.69	2.17
6	2.00	1.81	2.49	1.73	1.85
7	2.63	2.14	2.60	1.74	1.93
8	2.02	1.46	4.33	1.03	2.14
9	2.48	2.04	3.41	2.26	3.87
10	1.87	1.58	3.43	2.31	1.65
Mean	2.54	1.86	2.71	1.90	2.21
SEM	0.18	0.11	0.32	0.17	0.20

Table ix Tryptophan hydroxylase enzyme (TPH) / β-actin protein levels of estrogen treated ovariectomized ($Ovx+E_2$), ovariectomized (Ovx), and proestrous (Pro) rats in midbrain.

No	$Ovx+E_2$	Ovx	Pro
1	0.59	1.01	0.62
2	0.13	0.87	0.21
3	0.42	0.70	0.35
Mean	0.38	0.86	0.39
SEM	0.14	0.09	0.12

Table x Serotonin reuptake transporter (SERT) / β-actin protein levels of estrogen treated ovariectomized (Ovx+E_2), ovariectomized (Ovx), and proestrous (Pro) rats in frontal cortex, amygdala, hippocampus, nucleus accumbens, and septum.

Ovx+E_2	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	1.16	1.82	0.84	0.95	1.08
2	1.57	1.72	1.09	1.27	1.12
3	0.92	1.38	0.43	0.75	0.76
4	1.51		0.61	0.93	0.24
5			2.16	1.18	
Mean	1.29	1.64	1.03	1.02	0.80
SEM	0.15	0.13	0.30	0.09	0.20

Ovx	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	0.79	2.40	0.93	1.22	1.12
2	1.46	1.40	0.84	1.78	0.30
3	0.91	1.16	0.58	0.99	0.55
4	1.89		0.62	1.11	0.92
5			0.71	1.08	
Mean	1.26	1.66	0.74	1.23	0.72
SEM	0.26	0.38	0.07	0.14	0.18

Pro	Frontal cortex	Amygdala	Hippocampus	Nucleus accumbens	Septum
1	0.78	2.00	0.79	1.74	1.12
2	1.57	1.28	1.04	1.62	1.44
3	1.01	1.15	0.67	1.21	0.72
4	2.08		0.62	0.83	1.72
5			0.30	0.90	
Mean	1.36	1.48	0.68	1.26	1.25
SEM	0.29	0.26	0.12	0.18	0.21

Table xi Effect of 0.3 mg/kg ritanserin on baseline, avoidance 1, and 2 latency times of inhibitory avoidance task and escape latency times of one-way escape task in the elevated T-maze of estrogen treated ovariectomized ($Ovx+E_2$), ovariectomized (Ovx), and proestrous (Pro) rats.

$Ovx+E_2$	Baseline	Avoidance 1	Avoidance 2	Escape
1	14.41	133.31	128.59	12.66
2	22.19	107.22	18.53	25.09
3	6.09	7.35	10.88	5.29
4	10.66	82.06	161.68	3.10
5	32.34	84.40	176.75	15.68
6	5.37	10.54	55.57	33.81
Mean	15.18	70.81	92.00	15.94
SEM	4.26	20.98	29.82	4.80

Ovx	Baseline	Avoidance 1	Avoidance 2	Escape
1	70.53	238.87	249.28	14.69
2	37.97	40.09	31.31	14.63
3	11.38	300.00	250.41	5.56
4	22.25	32.03	109.35	11.00
5	52.47	75.28	85.78	33.78
6	71.91	199.66	211.00	3.69
7	12.53	260.37	217.66	12.00
8	11.16	156.69	145.12	10.84
Mean	36.28	162.87	162.49	13.27
SEM	9.18	36.68	28.93	3.24

Pro	Baseline	Avoidance 1	Avoidance 2	Escape
1	6.15	5.66	8.00	18.28
2	79.44	86.32	243.16	8.07
3	74.91	300.00	300.00	3.53
4	66.81	300.00	300.00	8.72
5	12.84	16.41	81.06	30.72
6	5.96	221.47	300.00	26.65
7	89.62	300.00	300.00	5.50
8	90.75	146.18	300.00	15.78
Mean	53.31	172.01	229.03	14.66
SEM	13.47	44.62	41.43	3.54

Table xii Effect of 1.0 mg/kg ritanserin on baseline, avoidance 1, and 2 latency times of inhibitory avoidance task and escape latency times of one-way escape task in the elevated T-maze of estrogen treated ovariectomized ($Ovx+E_2$), ovariectomized (Ovx), and proestrous (Pro) rats.

$Ovx+E_2$	Baseline	Avoidance 1	Avoidance 2	Escape
1	6.53	141.41	122.25	9.50
2	9.10	184.53	300.00	8.69
3	2.97	74.12	24.66	19.68
4	12.47	192.79	205.90	11.97
5	8.09	94.25	189.90	3.66
6	10.43	18.09	65.06	17.63
7	18.72	62.66	4.91	3.68
8	38.47	49.41	300.00	10.69
9	55.03	150.53	77.44	5.63
10	48.40	98.47	45.94	11.87
Mean	21.02	106.63	133.61	10.30
SEM	6.01	18.54	34.62	1.70

Ovx	Baseline	Avoidance 1	Avoidance 2	Escape
1	8.81	39.94	215.43	27.72
2	7.97	300.00	212.32	23.09
3	6.19	300.00	111.62	3.12
4	9.28	63.84	39.72	5.25
5	39.08	118.97	192.5	16.12
6	8.84	102.62	117.32	12.53
7	13.75	116.94	268.54	4.66
8	8.00	15.53	153.91	10.06
9	33.87	45.00	177.72	3.25
10	55.47	300.00	300.00	9.46
Mean	19.13	140.28	178.91	11.53
SEM	5.47	36.44	24.42	2.69

Pro	Baseline	Avoidance 1	Avoidance 2	Escape
1	5.22	56.25	186.03	2.56
2	7.59	26.47	242.31	7.60
3	11.34	122.22	55.09	2.97
4	9.28	146.91	300.00	22.35
5	44.50	254.88	300.00	4.34
6	72.35	299.38	300.00	6.10
7	5.31	177.78	237.38	9.60
8	18.81	65.19	300.00	16.93
Mean	21.80	143.64	240.10	9.06
SEM	8.55	34.27	30.33	2.50

Table xiii Effect of 3.0 mg/kg ritanserin on baseline, avoidance 1, and 2 latency times of inhibitory avoidance task and escape latency times of one-way escape task in the elevated T-maze of estrogen treated ovariectomized ($Ovx+E_2$), ovariectomized (Ovx), and proestrous (Pro) rats.

$Ovx+E_2$	Baseline	Avoidance 1	Avoidance 2	Escape
1	6.81	14.00	118.15	6.31
2	19.65	239.94	220.93	4.41
3	9.78	27.81	110.81	23.28
4	10.44	42.56	30.00	9.97
5	7.91	115.38	33.21	12.81
6	35.75	174.15	84.66	24.81
7	3.10	92.13	300.00	14.75
8	6.12	14.19	71.47	5.69
9	33.60	206.13	209.25	15.03
Mean	14.80	102.92	130.94	13.01
SEM	4.05	28.83	30.91	2.45

Ovx	Baseline	Avoidance 1	Avoidance 2	Escape
1	34.72	105.59	219.57	22.94
2	16.13	253.28	300.00	16.34
3	20.00	142.00	163.03	15.00
4	7.72	8.84	203.25	9.66
5	10.22	98.81	239.34	6.31
6	28.75	54.78	62.59	26.60
7	10.59	300.00	300.00	15.84
8	44.47	82.81	78.85	28.50
9	8.06	156.50	300.00	6.35
Mean	20.07	133.62	207.40	16.39
SEM	4.39	30.95	30.36	2.75

Pro	Baseline	Avoidance 1	Avoidance 2	Escape
1	29.37	17.00	156.59	22.53
2	9.12	50.31	10.53	17.38
3	10.57	14.07	75.96	9.94
4	12.03	52.62	88.97	5.00
5	6.87	8.21	49.66	16.22
6	13.03	7.50	123.97	2.85
7	6.50	9.19	225.65	10.41
8	6.66	25.85	8.63	32.44
9	32.00	166.56	44.60	17.75
Mean	14.02	39.03	87.17	14.95
SEM	3.25	16.95	23.79	3.05

Table xiv Effect of 0.3 mg/kg ritanserin on total numbers of crosses, number of first 30 seconds crosses, time in outer zone, and time in inner zone of open field test of estrogen treated ovariectomized (Ovx+E_2), ovariectomized (Ovx), and proestrous (Pro) rats.

Ovx+E_2	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	112	26	175.13	124.87
2	136	23	201.97	98.03
3	142	25	238.15	61.85
4	101	23	274.40	25.60
5	180	25	220.47	79.53
6	106	23	198.39	101.61
Mean	129.50	24.17	218.09	81.92
SEM	12.14	0.54	14.23	14.23

Ovx	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	146	12	235.35	64.65
2	116	16	182.92	117.08
3	105	24	219.24	80.76
4	74	19	135.17	164.83
5	122	20	214.29	85.71
6	87	21	268.95	31.05
7	91	22	211.00	89.00
8	101	19	215.72	84.28
Mean	105.25	19.13	210.33	89.67
SEM	8.00	1.32	13.75	13.75

Pro	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	100	27	213.52	86.48
2	94	19	106.54	193.46
3	114	25	272.95	27.05
4	120	22	224.52	75.48
5	144	21	158.81	141.19
6	145	22	270.27	29.73
7	133	28	226.49	73.51
8	101	4	269.29	30.71
Mean	118.88	23.43	217.80	82.20
SEM	7.11	1.25	20.89	20.89

Table xv Effect of 1.0 mg/kg ritanserin on total numbers of crosses, number of first 30 seconds crosses, time in outer zone, and time in inner zone of open field test of estrogen treated ovariectomized (Ovx+E_2), ovariectomized (Ovx), and proestrous (Pro) rats.

Ovx+E_2	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	122	18	168.97	131.03
2	73	23	259.87	40.13
3	118	21	277.66	22.34
4	109	23	246.27	53.73
5	107	18	257.15	42.85
6	56	19	59.65	240.35
7	155	19	238.19	61.81
8	82	22	211.54	88.46
9	139	25	259.70	40.30
10	102	20	248.72	51.28
Mean	106.30	20.80	222.77	77.23
SEM	9.48	0.76	20.56	20.56

Ovx	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	95	25	181.35	118.65
2	82	16	296.05	3.95
3	139	27	189.39	110.61
4	99	24	112.85	187.15
5	120	22	254.81	45.19
6	104	19	203.92	96.08
7	130	21	267.00	33.00
8	109	19	273.46	26.54
9	149	23	258.00	42.00
10	121	19	255.92	44.08
Mean	114.80	21.50	229.28	70.73
SEM	6.60	1.06	17.67	17.67

Pro	Total crosses	1st 30s crosses	Outer zone (s)	Inner zone (s)
1	121	19	256.44	43.56
2	67	17	280.57	19.43
3	135	22	216.56	83.44
4	44	19	211.75	88.25
5	103	19	154.36	145.64
6	81	21	167.72	132.28
7	136	25	187.28	112.72
8	129	24	224.10	75.90
Mean	102.00	20.75	212.35	87.65
SEM	12.22	0.98	15.08	15.08

Table xvi Effect of 3.0 mg/kg ritanserin on total numbers of crosses, number of first 30 seconds crosses, time in outer zone, and time in inner zone of open field test of estrogen treated ovariectomized (Ovx+E_2), ovariectomized (Ovx), and proestrous (Pro) rats.

Ovx+E_2	Total crosses	1^{st} 30s crosses	Outer zone (s)	Inner zone (s)
1	117	23	202.97	97.03
2	158	31	149.17	150.83
3	65	20	266.09	33.91
4	115	25	139.74	160.26
5	58	23	252.62	47.38
6	98	23	260.91	39.09
7	135	33	263.27	36.73
8	130	21	137.91	162.09
9	73	28	288.90	11.10
Mean	105.44	25.22	217.95	82.05
SEM	11.46	1.50	20.39	20.39

Ovx	Total crosses	1^{st} 30s crosses	Outer zone (s)	Inner zone (s)
1	122	22	192.90	107.10
2	147	21	226.04	73.96
3	151	21	207.61	92.39
4	121	23	121.88	178.12
5	112	27	77.81	222.19
6	100	25	67.78	232.22
7	142	23	231.21	68.79
8	62	16	71.49	228.51
9	89	25	286.35	13.65
Mean	116.22	22.56	164.79	135.21
SEM	9.75	1.06	27.15	27.15

Pro	Total crosses	1^{st} 30s crosses	Outer zone (s)	Inner zone (s)
1	67	21	87.75	212.25
2	117	25	207.52	92.48
3	101	20	79.77	220.23
4	125	24	111.48	188.52
5	128	29	277.46	22.54
6	152	29	262.71	37.29
7	138	27	274.19	25.81
8	127	34	231.71	68.29
9	85	21	118.61	181.39
Mean	115.56	25.56	183.47	116.53
SEM	8.91	1.55	27.78	27.78

Table xvii Values of standard 5-HT and 5-HIAA for calculation of standard curve using in HPLC technique.

5-HT (nM)	Area under curve of 5-HT/DHBA		
	1st injection	2nd injection	Average
10	0.36	0.38	0.37
20	0.66	0.64	0.65
100	3.06	3.25	3.16
200	8.18	7.74	7.96
500	18.40	17.38	17.89
1000	35.83	27.79	31.81

$y = 0.0328x$, $R^2 = 0.9933$

5-HIAA (nM)	Area under curve of 5-HIAA/DHBA		
	1st injection	2nd injection	Average
10	0.18	0.35	0.27
20	0.53	0.56	0.55
100	2.25	2.38	2.32
200	5.31	5.01	5.16
500	11.74	10.93	11.34
1000	22.68	20.22	21.45

$y = 0.0218x$, $R^2 = 0.9971$

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P-10

DIFFERENT EFFECTS OF CHRONIC ESTROGEN ADMINISTRATION AND NATURAL HIGH LEVELS OF ESTROGEN ON ANXIETY-LIKE BEHAVIORS IN THE ELEVATED T-MAZE

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SUMMARY

It is widely accepted that estrogen could modulate anxiety; however, the effects are still controversial. In this study, the effect of estrogen on anxiety-liked behavior was tested with the elevated T-maze (ETM) in ovariectomized rats treated with estrogen (10 μg/kg, daily; Ovx+E_2) or without estrogen (Ovx), and the proestrous rats (Pro; the naturally high level of estrogen). The ETM is based on the assumption that inhibitory avoidance and one way escape are respectively related to generalized anxiety disorder (GAD) and panic disorder (PD). Four weeks after ovariectomy, the ETM data showed that the inhibitory avoidance was impaired in Ovx+E_2 rats and the escape latency was prolonged in Pro rats. Additionally, the Ovx+E_2 rats spent more time in the inner zone of the open field test, while the overall locomotor activity was unaffected by estrogen. These data suggested that these two forms of anxiety, GAD and PD were differently modulated by estrogen as shown in Ovx+E_2 and Pro rats, respectively.

INTRODUCTION

Presently, we know that estrogen plays an important role in the modulation of anxiety. The menopausal women show symptoms of depression, anxiety, and cognitive dysfunction in which can be reversed by estrogen replacement therapy (Arpels, 1996; Halbreich, 1997; Sherwin, 1998). In rodents, several studies have indicated that proestrous female rats with the highest level of estrogen, showed their anxiolytic-like behavior when tested with the elevated plus-maze (EPM) (Marcondes et al., 2001; Mora et al., 1996). Interestingly, chronic estrogen treatment in the Ovx animals documented estrogen to act either as an anxiogenic or anxiolytic when tested with the EPM (Morgan and Pfaff, 2002; Koss et al., 2004). These variations may be related to the different types of anxiety, i.e. panic, phobia, and generalized anxiety reflected by different behavioral models of anxiety.

In 1993, Graeff and co-workers (1993) developed the ETM that can separate different types of anxiety. Since the EPM cannot separate different types of fear, it was classified as a "mixed" test of anxiety. This may be responsible for the inconsistency results of anxiolytic or anxiogenic effects of estrogen in the EPM. Contrarily, the ETM has been proposed to evaluate two types of anxiety in the same animal, i.e. learned (or conditioned) anxiety, represented by inhibitory avoidance behavior, and innate (or unconditioned) fear, represented by one-way escape (Graeff et al., 1993; Zangrossi and Graeff, 1997). Inhibitory avoidance was impaired by agents that were effective in GAD patients (Graeff et al., 1997). Thus, the learned nature and its pharmacological sensitivity suggest that this behavior is related to GAD. Similarly, one-way escape was increased by agents that were effective in PD patients. Therefore, based on the assumption that innate fear is related to PD and on the pharmacological sensitivity of PD, one-way escape is supposed to represent panic anxiety (Zangrossi and Graeff, 1997).

Therefore, the present study was aimed to investigate the effects of chronic dose of estrogen on the Ovx rats compared with natural high levels of estrogen in Pro rats by using the ETM for measuring anxiety-like behaviors in rats.

MATERIALS AND METHODS

Animals and hormone administration

Adult female Wistar rats were obtained from National Laboratory Animal Center, Mahidol University, Thailand. All rats were maintained at 25±2°C on 12-h light/dark cycle and given standard rat chow and water ad libitum. All rats were either bilaterally ovariectomized or sham operated under anesthesia. The Ovx+E_2 rats were injected with estrogen (17β-estradiol 10 µg/kg, s.c. daily), whereas the Ovx and Pro rats were subcutaneously injected with an equivalent volume of the propylene glycol. Their uterine weights were measured for determining the effectiveness of ovariectomy and estrogen replacement. All procedures were done under the approval of Animal Used Committee, Faculty of Veterinary Science, Chulalongkorn University. There were 10-11 animals in each group.

Elevated T-maze test

Four weeks after ovariectomy, all rats were tested with the ETM. The ETM consisted of two open arms and one enclosed arm perpendicular to the opened arms and the apparatus was elevated above the floor. The test session consisted of three inhibitory avoidance trials and one escape trial held at 30-s intervals. On the first inhibitory avoidance trial, rat was placed at the end of the enclosed arm. The baseline latency was defined as the time(s) required for the rat to exit this arm with four paws. The same measurement was repeated in two subsequent trials (avoidance 1 and 2). Following avoidance training, the escape trial was done. The animal was placed at the end of the right open arm and the time(s) required for the rat to exit this arm with four paws recorded as escape latency.

Open field test

After the ETM session, the animals were tested in the open field for 5 min. The open field was a wooden box with squares grid floor. All but the peripheral squares were considered as inner zone. The numbers of total crosses that the rat made during the 5 min were recorded as the locomotor activity. Times spent in the inner zone were considered indicative of anti-anxiety behavior in the rodent.

Statistical analysis

The avoidance latency in the ETM was analyzed by split-plot analysis of variance (ANOVA) with treatment as the independent factor and trials (baseline, avoidance 1, and 2) as the dependent factor. In case of significant effect of treatment or of treatment versus trials interaction, data were analyzed by one-way ANOVA followed by the Duncan post hoc test. Other data were submitted to one-way ANOVA followed by the Duncan post hoc test. In all cases, a value of $P< 0.05$ was considered significant.

RESULTS

Elevated T-maze test

As illustrated in Fig. 1A, the inhibitory avoidance in the ETM was impaired in Ovx+E_2 rats. Split-plot ANOVA showed a significant effect of treatment [$F(2, 30) = 5.19$, $P < 0.05$] and trials [$F(2, 60) = 18.67$, $P < 0.001$]. The Duncan post hoc test showed that in the avoidance 2, the Ovx+E_2 group decreased the latency to leave the enclosed arm, when compared to Ovx and Pro rats ($P < 0.05$). Moreover, the Pro rats significantly increased the escape latency [$F(2, 30) = 6.79$, $P < 0.01$] from the open arm (Fig. 1B).

Open field test

Locomotor activity in the open field (Fig. 2A) did not differ among groups as indicated by the same total crosses [$F(2, 29) = 1.60$, NS]. One-way ANOVA showed a significant effect of treatment [$F(2, 29) = 3.95$, $P < 0.05$]. The Duncan post hoc test showed that Ovx+E_2 rats spent more time in the inner zone and less time in outer zone of the open field when compared with another two groups ($P < 0.05$) (Fig. 2B).

DISCUSSION

The ETM data revealed that Ovx+E_2 animals impaired inhibitory avoidance as compared with Ovx and Pro rats indicating a lower GAD in Ovx+E_2 rats than others. Whereas the Pro rats showed high levels of GAD, but showed impaired one-way escape suggesting the low levels of PD. Additionally, the open field data demonstrated that the Ovx+E_2 group had the anxiolytic-like behavior by increasing the time spent in the inner zone. One possible explanation of the Pro group did not show the anxiolytic-like behavior in the open field, it could be that this test was only

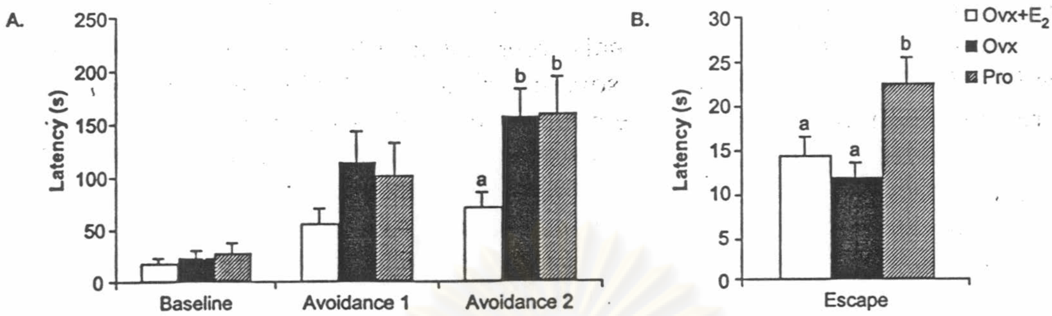

FIGURE 1. The ETM test. Different letters indicate statistical differences among groups.

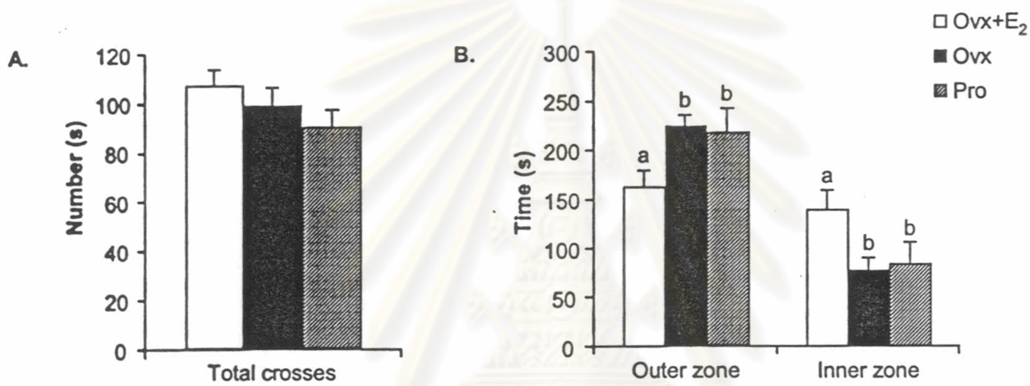

FIGURE 2. The open field test. Different letters indicate statistical differences among groups.

effective to GAD. Since the total numbers of crosses in open field arena, indicated of locomotor activity was unaffected in both Ovx+E_2 and Pro rats, this confirmed that the changes in ETM were not due to changes in locomotor activity.

Regarding the hypothesis of Deakin and Graeff (1991) about the dual roles of 5-HT regulating anxiety-like behavior, they proposed that 5-HT facilitates conditioned responses to aversive stimuli related to GAD through the forebrain structures such as the septo-hippocampal system and the amygdala, and 5-HT inhibits unconditioned fight/flight responses related to PD through the periaqueductal grey (PAG) in the brainstem. Moreover, there are many evidences reported that estrogen can facilitate the serotonergic system in many processes including serotonin synthesis, reuptake, degradation, and receptor activation [reviewed by Bethea et al. (2002)]. From these evidences, our results could be explained by that estrogen in the Ovx+E_2 rats may decrease the 5-HT activity through the forebrain areas to reduce GAD while in the Pro rats increase 5-HT activity through PAG area to reduce PD. Since it is now known that estrogen can regulate neuronal activity via both genomic and non-genomic pathways [reviewed by McEwen (2002)], the different mechanism of estrogen on serotonergic neuron could therefore lead to different findings between Ovx+E_2 and Pro rats in this study. In conclusion, the present results suggest the roles of estrogen to anti-GAD in chronic estrogen treated Ovx rats and to anti-PD in the natural high levels of estrogen in proestrous female rats. Nevertheless, the mechanisms of these phenomenons of estrogen in controlling anxiety necessitate future studies especially in the field of serotonergic system. Currently, the role of estrogen in Ovx rats and Pro rats on the serotonergic neurotransmission in the brain areas that related to the anxiety-like behaviors is being investigated in our laboratory.

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