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Pentylenetetrazol-Induced Kindling in Rats: Effect of GABA Function Inhibitors

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CORDA, M. G., M. ORLANDI, D. LECCA, G. CARBONI, V. FRAU AND O. GIORGI. *Pentylenetetrazol-induced kindling in rats: Effect of GABA function inhibitors.* PHARMACOL BIOCHEM BEHAV **40**(2) 329–333, 1991.—The repeated administration of subconvulsant doses of pentylenetetrazol (PTZ) produced a progressive sensitization to the effects of this compound (i.e., chemical kindling) in the rat. A very similar time-course for PTZ-induced kindling was observed using two different treatment schedules: 1) one injection every day (30 mg/kg, IP), and 2) one injection (30 mg/kg, IP) every second day. When these treatment schedules were used for eight consecutive weeks, more than 80% of the rats displayed convulsions by the end of treatment. In contrast, only 20% of the rats were sensitized if PTZ was administered twice daily at the dose of 15 mg/kg, IP. The increased sensitivity to the convulsant effect of PTZ was still present one year after completion of the chronic treatment. Moreover, rats kindled with PTZ showed an enhanced susceptibility to convulsions induced by different inhibitors of central GABAergic function, such as the chloride channel blocker picrotoxin, the benzodiazepine receptor ligands FG 7142 and Ro 15-4513, and the inhibitor of GABA synthesis isoniazid. In contrast, the sensitivity to the convulsant action of the glycine receptor antagonist strychnine was unchanged by repeated PTZ administration. It is suggested that kindling produced by PTZ may be associated with a persistent reduction in the inhibitory function of the GABAergic system in the brain.

Pentylenetetrazol (PTZ) Chemical kindling Convulsions β-Carbolines Picrotoxin Isoniazid GABA

THE kindling phenomenon, originally described by Goddard (11), is now generally accepted as an experimental model of epilepsy and epileptogenesis. This model is characterized by an increased susceptibility to seizures after repeated brain stimulation with subconvulsive electric stimuli. Kindled seizures can be induced in a number of species, including rats and mice, by electrical stimulation of different brain areas such as the amygdala, the hippocampus and the frontal cortex (12, 19, 27). More recently, it has been shown that an effect comparable to electric kindling can be induced by the repeated administration of subconvulsant doses of central nervous system stimulants. Thus, a progressive development of seizures, i.e., chemical kindling, is observed after the systemic administration of carbamylcholine, cocaine, N-methyl-β-carboline-3-carboxamide (FG 7142), picrotoxin and pentylenetetrazol (PTZ) (5, 8, 20, 22, 24, 25, 29).

PTZ has been widely used in experimental models of epilepsy and anxiety. On acute administration, this compound has a proconflict effect and induces convulsions in rats and mice (4,31). A number of studies indicate that its pharmacological effects are mediated via a specific interaction with the GABA-coupled chloride ionophore. Thus PTZ antagonizes the effect of GABA on chloride channel conductance in spinal cord neurones and inhibits the binding of ^{35}S-t-butylbicyclophosphorothionate (^{35}S-TBPS) to the chloride channel in brain membrane preparations (7, 21, 28).

The purpose of the present study was to characterize further the experimental conditions necessary to induce PTZ-kindling in rats. Moreover, since there is extensive evidence that the GABAergic system plays an important role in convulsive disorders, it was considered of interest to evaluate the efficacy of different GABA-function inhibitors at inducing convulsions in PTZ-kindled rats.

METHOD

Animals

Male Sprague-Dawley CD rats (Charles River, Como, Italy) weighing 250–300 g at the beginning of the chronic treatment were housed six per cage under controlled temperature and lighting (light period: 8.00 a.m.–8.00 p.m.), with food and water freely available.

Chronic Treatment and Behavioural Observation

PTZ was given intraperitoneally using three different treatment schedules: 1) 15 mg/kg twice a day (8.00 a.m. and 8.00 p.m.), 2) 30 mg/kg once a day (at 9.00 a.m.), and 3) 30 mg/kg every second day (i.e., three times a week) at 10 a.m., for up to eight consecutive weeks. Control rats received an equivalent volume of saline (2 ml/kg, IP). Rats were observed in open top cages for one hour after each injection, except those treated twice a day, which were observed only after the morning injection. Seizures were recorded according to the following scale: 0, no response; 1, ear and facial twitching; 2, one to twenty myo-

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clonic body jerks in ten minutes; 3, more than twenty myoclonic body jerks in ten minutes; 4, clonic forelimb convulsions; 5, generalized clonic convulsions with rearing and falling down episodes; 6, generalized convulsions with tonic extension episodes and status epilepticus. Animals that had a seizure score of 5 or 6 after three consecutive injections of PTZ were defined as kindled, and their treatment was discontinued.

Seizure Studies

These experiments were performed using 80 kindled rats that had been treated with PTZ 30 mg/kg IP three times a week until the kindling criterion was reached (six to eight weeks). Unless otherwise stated, rats were challenged only once.

Challenge with PTZ. Three days after the completion of the chronic treatment, groups of control and PTZ-kindled rats were challenged with 30 mg/kg PTZ or with its solvent (saline). Since the challenge with PTZ solvent failed to produce a behavioral effect, the experimental groups of chronic saline plus acute saline and chronic PTZ plus acute saline were not included in subsequent experiments. Other groups of control and PTZ-kindled rats were challenged with 20 mg/kg of PTZ at three, six, or twelve months after completion of the chronic treatment. A lower dose of PTZ was used in the latter experiments taking into account the age-related increase in the sensitivity to the convulsant effects of this agent (our unpublished results). Rats were placed in open top cages and observed for one hour after each challenge injection in order to determine the incidence of the various types of convulsions.

Challenge with picrotoxin, FG 7142 and Ro 15-4513. Three days after the last PTZ administration, rats were challenged with picrotoxin (1.5 mg/kg, IP), FG 7142 (30 mg/kg, IP) or Ro 15-4513 (20 mg/kg, IP). Rats challenged with picrotoxin and with FG 7142 were tested again with the same drug (one month later for picrotoxin 1.5 mg/kg and 6 months later for FG 7142). A smaller dose of FG 7142 (10 mg/kg, IP) was used for the second challenge because of the increased sensitivity to this drug in older animals (our unpublished results). Animals were observed for one hour after the injection and the incidence of convulsions was recorded.

Challenge with isoniazid. Isoniazid was injected subcutaneously at the dose of 200 mg/kg, at three or thirty days after the last PTZ administration. Animals were observed for three hours after the injection and the incidence of clonic convulsions, tonic extensions, and mortality was recorded.

Challenge with strychnine. Strychnine (1.2 mg/kg) was administered subcutaneously three days after the completion of the chronic treatment. Rats were observed for the appearance of convulsions for one hour thereafter and the latency to the first seizure and the number of convulsing rats were recorded.

Statistics

The different curves of sensitization to PTZ as a function of the treatment schedule were compared with the Kruskal-Wallis analysis by ranks. The effects of proconvulsant and convulsant drugs during withdrawal from chronic treatment with PTZ or saline were analyzed using the Fisher's exact probability test.

Drugs

FG 7142 (N-methyl-β-carboline-3-carboxamide) was a generous gift from Dr. D. Stephens (Schering AG, Berlin, Germany) and Ro 15-4513 (ethyl-8-azido-5, 6-dihydro-5-methyl-6-oxo-4H-imidazo-(1,5-a)(1,4)-benzodiazepine-3-carboxylate) was kindly donated by Hoffmann-La Roche (Basel, Switzerland). Both drugs were suspended in distilled water with 50 μl of Tween 80 per 5 ml. Pentylenetetrazol (PTZ), isonicotinic acid hydrazide (isoniazid), picrotoxin, and strychnine were purchased from Sigma Chemical Co. (St. Louis, MO). The above drugs were dissolved in saline.

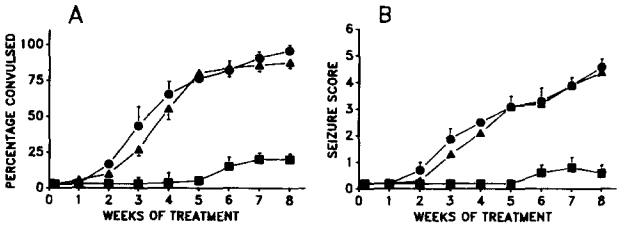

FIG. 1. Time-course for pentylenetetrazol production of kindling using three different treatment schedules. PTZ was administered IP at the dose of 30 mg/kg once a day at 9 a.m. (filled triangles) or three times a week at 10 a.m. (filled circles). Another group received PTZ at the dose of 15 mg/kg twice daily at 8.00 a.m. and 8.00 p.m. (filled squares). The results are expressed as the percentage of the total number of treated rats displaying convulsions in panel A and as the mean seizure score for each week of treatment in panel B. Values are the mean ± S.E.M. of three (filled circles) or seven (filled triangles and filled squares) observations per week. The number of animals per group was: 20 (PTZ three times a week), 15 (PTZ once daily) and 15 (PTZ twice a day).

RESULTS

The time-course of the development of kindling induced by the administration of PTZ using three different treatment schedules is shown in Fig. 1. Rats injected with PTZ (30 mg/kg, IP) once a day or once every second day (i.e., three times a week) showed convulsions starting from the second week of treatment until 80–90% of them were affected by the eighth week (Fig. 1A). By contrast, convulsions were not observed in rats receiving 15 mg/kg of PTZ twice daily until the sixth week of treatment and only 20% of the animals were affected by the eighth week (Fig. 1A). The intensity of the convulsions increased with the repeated administration of PTZ 30 mg/kg, IP once daily or three times a week, as reflected by the progressive increment in the seizure score (Fig. 1B). In fact, until the second week of treatment, rats had only brief and repeated myoclonic jerks of the head and body, which appeared 5 to 10 minutes after the injection and lasted for 45 to 60 minutes. In the following weeks, an increasing number of rats exhibited also clonic and clonic-tonic convulsions. In some cases, seizures terminated in exitus due to respiratory arrest (mortality rate: 15% to 20%, data not shown). By the end of the chronic treatment, the mean seizure score was 4.4 ± 0.1 in rats injected once daily and 4.6 ± 0.3 in rats injected three times a week (Fig. 1B). On the other hand, the mean seizure score after eight weeks of treatment with PTZ 15 mg/kg, IP once daily was less than 1 (Fig. 1B). A Kruskal-Wallis analysis by ranks revealed no difference between one daily injection and three weekly injections, whereas both schedules induced a more intense sensitization as compared with two daily injections ($p<0.001$). Finally, the repeated administration of saline failed to induce convulsions throughout the eight weeks of treatment (not shown).

A remarkable difference in the rate of appearance of kindling in rats treated with 30 mg/kg once daily versus three times a week became apparent when the number of injections rather than the number of weeks of treatment was considered (Fig. 2). In

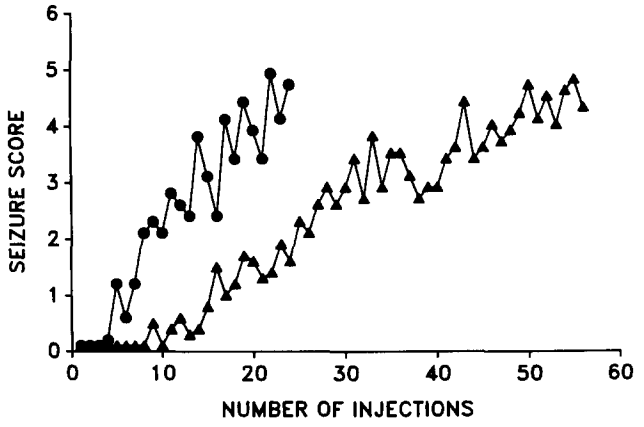

FIG. 2. Development of kindling as a function of the number of injections of pentylenetetrazol. PTZ was administered IP at the dose of 30 mg/kg once every day (filled triangles) or three times a week (filled circles). The results are expressed as the mean seizure score of 20 rats (filled circles) or of 15 rats (filled triangles).

fact, rats receiving PTZ three times a week required an average of 13 to 15 injections to reach a high degree of sensitization (mean seizure score of 3 or more), whereas the rats treated with PTZ on a daily basis achieved a similar seizure score after 29 to 35 injections. Since fewer injections were required to induce kindling when PTZ was administered three times a week, this treatment schedule was used in all subsequent studies.

The persistence of kindling upon completion of the chronic treatment was evaluated by administering a challenge dose of PTZ to rats chronically treated with saline or PTZ at different times after withdrawal. The results shown in Table 1 indicate that PTZ-kindled rats showed an enhanced sensitivity to the drug for as long as one year after completion of the chronic treatment. In contrast, rats treated chronically with saline were only marginally affected by the PTZ challenge. Finally, a challenge with saline to rats repeatedly injected with saline or PTZ failed to produce any behavioral effect, thus excluding the possibility that the injection itself, rather than the convulsant, could account for the kindling phenomenon (Table 1).

We also evaluated the sensitivity of PTZ-kindled rats to the effects of proconvulsant and convulsant drugs known to reduce the GABAergic transmission. Table 2 shows the effects of a challenge with the chloride channel blocker picrotoxin or the benzodiazepine receptor ligands FG 7142 and Ro 15-4513 on saline or PTZ-kindled rats at three days after withdrawal. All these compounds were almost completely inactive in rats repeatedly injected with saline, but were able to induce convulsions in PTZ-treated rats at three days after withdrawal (Table 2). Moreover, the enhanced sensitivity to picrotoxin and to FG 7142 persisted for one month and six months, respectively (Table 2).

Finally, we examined the susceptibility to convulsions induced by isoniazid in rats kindled with PTZ. Isoniazid was administered subcutaneously at the dose of 200 mg/kg to saline or PTZ-treated rats, three days after the completion of the chronic treatment. As shown in Fig. 3, isoniazid produced clonic convulsions in 80% and 93% of saline- and PTZ-treated rats, respectively, whereas tonic extension episodes were present in 26% and 80% of saline- and PTZ-treated rats, respectively. In addition, the mortality rate was 13% in the saline group, whereas 66% of PTZ-kindled rats died. Similar results were obtained in separate groups of rats challenged with isoniazid 30 days after the last PTZ administration (Fig. 3). By contrast, the latency and the incidence of convulsions induced by strychnine (1.2 mg/kg, SC) were not different in rats chronically treated with PTZ as compared with saline-treated controls (Table 3).

TABLE 1

EFFECT OF A CHALLENGE DOSE OF PENTYLENETETRAZOL (PTZ) IN RATS REPEATEDLY INJECTED WITH SALINE OR PTZ

Chronic Treatment	Time After Last Treatment	Challenge	Dose (mg/kg)	No. of Animals Showing Convulsions
Saline	3 days	Saline	—	0/5
Saline	3 days	PTZ	30	1/10
PTZ	3 days	Saline	—	0/5
PTZ	3 days	PTZ	30	10/10†
Saline	3 months	PTZ	20	2/10
PTZ	3 months	PTZ	20	9/10†
Saline	6 months	PTZ	20	2/8
PTZ	6 months	PTZ	20	8/8†
Saline	12 months	PTZ	20	0/6
PTZ	12 months	PTZ	20	5/6*

Rats were chronically treated with saline or PTZ as described in the Method section and were challenged with PTZ at different times after drug discontinuation. Shown are the number of rats with a seizure score of 2 or more after each challenge. *$p<0.01$; †$p<0.005$ vs. the respective saline-PTZ group (Fisher's exact probability test).

DISCUSSION

The present data provide a detailed characterization of the experimental conditions required to induce chemical kindling with PTZ in rats. The effects of different GABA function inhibitors on PTZ-kindled rats were also evaluated.

In the initial studies on PTZ-induced kindling adequate control groups were not included in the experimental design (22,24). Therefore, it has been argued that the enhanced susceptibility to convulsions could be an artifact of the injection procedure (16) or the consequence of an age-related increase in body weight (23) rather than a true kindling phenomenon. In contrast with

TABLE 2

EFFECT OF A CHALLENGE DOSE OF PICROTOXIN, FG 7142 OR Ro 15-4513 ON PENTYLENETETRAZOL-KINDLED RATS

Chronic Treatment	Time After Last Treatment	Challenge	Dose (mg/kg)	No. of Animals Showing Convulsions
Saline	3 days	Picrotoxin	1.5	0/6
PTZ	3 days	Picrotoxin	1.5	5/6*
Saline	1 month	Picrotoxin	1.5	2/6
PTZ	1 month	Picrotoxin	1.5	6/6*
Saline	3 days	FG 7142	30	0/8
PTZ	3 days	FG 7142	30	6/8*
Saline	6 months	FG 7142	10	1/7
PTZ	6 months	FG 7142	10	6/7*
Saline	3 days	Ro 15-4513	20	0/5
PTZ	3 days	Ro 15-4513	20	5/5*

Rats were treated with saline or PTZ as described in the Method section. Shown are the number of rats with a seizure score of 2 or more after each challenge. *$p<0.05$ vs. the respective saline-treated group (Fisher's exact probability test).

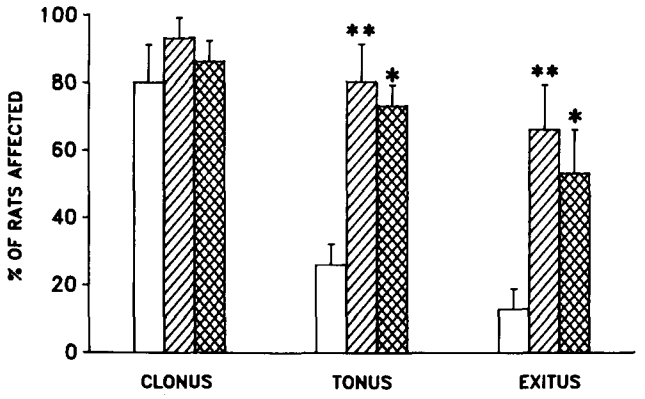

FIG. 3. Increased sensitivity to convulsions induced by isoniazid in rats kindled with pentylenetetrazol. Saline- (open columns) and PTZ-treated rats were challenged with isoniazid (200 mg/kg, SC) three days (striped columns) or thirty days (cross-hatched columns) after the last injection. Control values at three and thirty days were not statistically different from each other and were, therefore, pooled together. Results are expressed as the percentage of the total number of rats affected and are the means ± S.E.M. of data obtained in three independent experiments using five rats per experimental group. *$p<0.05$; **$p<0.005$ vs. the saline group (Fisher's exact probability test).

this possibility, our data confirm the initial (22,24) and the subsequent reports (9, 10, 18) indicating that the enhanced susceptibility to convulsions is the consequence of the chronic administration of PTZ since it is not present in rats repeatedly injected with saline and challenged with PTZ at different times after saline discontinuation.

The studies on the influence of the interdose interval on the development of kindling indicate that drug accumulation in brain does not play a role in PTZ-kindling, since fewer injections were necessary to sensitize rats to the same extent when PTZ was given three times a week as compared with daily injections. Our results also indicate that the interdose interval is a critical factor in the development of kindling. Accordingly, it has been suggested that the "intermittent" administration of a drug may be more efficacious in producing sensitization than the "continuous" administration (26). Similar results have been obtained with the electrical kindling of the amygdala. In fact, it has been shown that the repeated and intermittent stimulation of the amygdala at daily or weekly intervals would eventually lead to the development of major motor seizures to a previously subthreshold stimulus, whereas a more frequent electrical stimulation (i.e., every twelve hours or less) would retard the development of kindling (13). Another striking similarity between electrical kindling and PTZ-induced kindling is that both phenomena are long-lasting. In fact, in agreement with a previous study (10), we found an enhanced sensitivity to convulsions in rats challenged with PTZ as long as one year after drug discontinuation, suggesting that this treatment produces a permanent change in seizure susceptibility.

TABLE 3

EFFECT OF A CHALLENGE DOSE OF STRYCHNINE IN RATS REPEATEDLY INJECTED WITH SALINE OR PENTYLENETETRAZOL

Chronic Treatment	Latency (min)	No. of Rats Showing Convulsions
Saline	33 ± 5	3/7
PTZ	38 ± 7	4/7

Rats were treated with saline or PTZ as described in the Method section and were challenged with strychnine (1.2 mg/kg, SC) three days after the last drug administration.

Compelling evidence suggests that a reduction in GABA-mediated inhibitory transmission may be involved in seizures and epilepsy. Thus a variety of factors which decrease GABAergic function increase seizure susceptibility, whereas pharmacological manipulations which enhance GABAergic function reduce the incidence of seizures (14,15). A number of studies have also shown alterations in GABAergic parameters in the kindling model of epilepsy. In fact, the activity of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) and GABA levels are selectively decreased in discrete brain areas of electrically kindled rats (3). In addition, recent data indicate a subsensitivity of the $GABA_A$ receptor complex in the brain of kindled rats, as revealed by a reduction in the density of $GABA_A$ and benzodiazepine receptors, and in GABA-dependent chloride uptake (3,17). Moreover, the reduction in GABAergic parameters in the brain of kindled rats is in agreement with pharmacological data showing that the blockade of the GABAergic system accelerates kindling, whereas the enhancement of GABAergic activity retards and reverses it (3,17). In line with the above data, our results indicate that kindling induced by PTZ is associated with an enhanced sensitivity to the convulsant effect of GABA function inhibitors such as isoniazid, picrotoxin, FG 7142 and Ro 15-4513.

Isoniazid inhibits the activity of GAD by interfering with the coenzymic function of pyridoxal phosphate (15). After the systemic administration of isoniazid, GABA levels are reduced in synaptoneurosomes of the cerebral cortex (30), as well as in homogenates of discrete brain areas such as the hypothalamus, limbic forebrain, globus pallidus, hippocampus, cerebral cortex, and cerebellum (15). There is a good correlation between the reduction in GABA levels in brain and the occurrence of myoclonic convulsions after isoniazid administration to rats (15). On the other hand, picrotoxin, FG 7142 and Ro 15-4513 inhibit GABAergic transmission through postsynaptic mechanisms. Thus picrotoxin is a selective blocker of the GABA-coupled chloride ionophore (28), whereas the negative modulatory effects of FG 7142 and Ro 15-4513 on the function of the $GABA_A$ receptor complex are mediated via interaction with the benzodiazepine recognition site (1,2). Accordingly, on acute administration picrotoxin, FG 7142 and Ro 15-4513 produce or facilitate convulsions and have a proconflict effect in the rat (4–6). In addition, the repeated administration of picrotoxin or FG 7142 produces chemical kindling in rats and mice (5, 8, 20). Therefore, our finding that rats kindled with PTZ show an enhanced susceptibility to convulsions induced by isoniazid, picrotoxin, FG 7142 and Ro 15-4513 is consistent with the hypothesis that a reduction in GABAergic inhibition plays an important role in PTZ-induced kindling. In line with this hypothesis, we have recently found a reduction in GABA-stimulated $^{36}Cl^-$ uptake and in the binding of ^{35}S-TBPS, a ligand for the GABA-gated chloride channel (28), in the cerebral cortex of PTZ-kindled rats (7). It is noteworthy that the enhanced sensitivity to convulsions induced by GABA function inhibitors persists for a long time after drug discontinuation, indicating an enduring change in GABAergic transmission in brain.

Finally, the finding that the glycine receptor antagonist strychnine is equally effective at inducing convulsions in saline- and PTZ-treated rats indicates that the enhanced sensitivity to convulsions induced by GABA function inhibitors in PTZ-kindled rats is not due to nonspecific alterations in seizure threshold.

In conclusion, our results indicate that kindling induced by PTZ in rats may prove to be a useful experimental model to study the involvement of the central GABAergic neurotransmission in epilepsy and epileptogenesis.

REFERENCES

1. Bonetti, P. E.; Polc, P.; Pieri, L. An azido analogue of the benzodiazepine antagonist Ro 15-1788 (Ro 15-4513) behaves as a partial inverse benzodiazepine agonist. Neurosci. Lett. 18:30; 1984.
2. Braestrup, C.; Honoré, T.; Nielsen, M.; Petersen, E. N.; Jensen, L. H. Ligands for benzodiazepine receptors with positive and negative efficacy. Biochem. Pharmacol. 33:859–862; 1984.
3. Burnham, W. M. The GABA hypothesis of kindling: Recent assays studies. Neurosci. Biobehav. Rev. 13:281–288; 1989.
4. Corda, M. G.; Biggio, G. Proconflict effect of GABA receptor complex antagonists. Reversal by diazepam. Neuropharmacology 25:541–544; 1986.
5. Corda, M. G.; Giorgi, O.; Biggio, G. Behavioural and biochemical evidence for a long-lasting decrease in GABAergic function elicited by chronic administration of FG 7142. Brain Res. 384:60–67; 1986.
6. Corda, M. G.; Giorgi, O.; Longoni, B.; Biggio, G. Ro 15-4513, a partial inverse agonist for benzodiazepine recognition sites, has proconflict and proconvulsant effects in the rat. Eur. J. Pharmacol. 159:233–239; 1989.
7. Corda, M. G.; Giorgi, O.; Longoni, B.; Orlandi, M.; Biggio, G. Decrease in the function of the γ-aminobutyric acid-coupled chloride channel produced by the repeated administration of pentylenetetrazol to rats. J. Neurochem. 55:1216–1221; 1990.
8. Corda, M. G.; Giorgi, O.; Orlandi, M.; Longoni, B.; Biggio, G. Chronic administration of negative modulators produces chemical kindling and $GABA_A$ receptor down regulation. In: Biggio, G.; Costa, E., eds. GABA and benzodiazepine receptor subtypes. New York: Raven Press; 1990:153–166.
9. Craig, C. R.; Colasanti, B. K. A study of pentylenetetrazol kindling in rats and mice. Pharmacol. Biochem. Behav. 31:867–870; 1989.
10. Diehl, R. G.; Smialowski, A.; Gotwo, T. Development and persistence of kindled seizures after repeated injections of pentylenetetrazol in rats and guinea pigs. Epilepsia 25:506–510; 1984.
11. Goddard, G. V. Development of epileptic seizures through brain stimulation at low intensity. Nature 214:1020–1021; 1967.
12. Goddard, G. V. The kindling model of epilepsy. Trends Neurosci. 6:275–279; 1983.
13. Goddard, G. V.; McIntyre, D. C.; Leech, C. K. A permanent change in brain function resulting from daily electrical stimulation. Exp. Neurol. 25:295–330; 1969.
14. Haefely, W. E. GABA and the anticonvulsant action of benzodiazepines and barbiturates. Brain Res. Bull. 5(Suppl. 2):873–878; 1980.
15. Horton, R. W. GABA and seizures induced by inhibitors of glutamic acid decarboxylase. Brain Res. Bull. 5(Suppl. 2):605–608; 1980.
16. Izquierdo, I.; Fernandez, J.; Oliveira, R.; Settineri, F. Effect of daily saline, drug or blank injections on the susceptibility to the convulsant effect of drugs. Pharmacol. Biochem. Behav. 3:721–722; 1975.
17. Kamphuis, W.; Lopes da Silva, F. H. The kindling model of epilepsy: the role of GABAergic inhibition. Neurosci. Res. Commun. 6:1–10; 1990.
18. Karler, R.; Murphy, V.; Calder, L. D.; Turkanis, S. A. Pentylenetetrazol kindling in mice. Neuropharmacology 28:775–780; 1989.
19. La Salle, G. L. G. Amygdaloid kindling in the rat: regional differences and general properties. In: Wada, J. A., ed. Kindling II. New York: Raven Press; 1981:31–47.
20. Little, H. J.; Nutt, D. J.; Taylor, S. C. Acute and chronic effects of the benzodiazepine receptor ligand FG 7142: proconvulsant properties and kindling. Br. J. Pharmacol. 83:951–958; 1984.
21. MacDonald, R. L.; Barker, J. L. Pentylenetetrazol and penicillin are selective antagonists of GABA-mediated postsynaptic inhibition in cultured mammalian neurones. Nature 267:720–721; 1977.
22. Mason, C. R.; Cooper, R. M. A permanent change in convulsive threshold in normal and brain-damaged rats, with repeated small doses of pentylenetetrazol. Epilepsia 13:663–674; 1972.
23. Nutt, D. J.; Cowen, P. J.; Batts, C. C.; Grahame-Smith, D. G.; Green, A. R. Repeated administration of subconvulsant doses of GABA antagonist drugs. I. Effect on seizure threshold (kindling). Psychopharmacology (Berlin) 76:84–87; 1982.
24. Pinel, J. P. J.; Van Oot, P. H. Generality of the kindling phenomenon: some clinical implications. Can. J. Neurol. Sci. 2:467–475; 1975.
25. Post, R. M. Progressive changes in behaviour and seizures following chronic cocaine administration: relationship to kindling and psychosis. In: Ellinwood, E. H.; Kilbey, M. M., eds. Cocaine and other stimulants. New York: Plenum; 1977:353–372.
26. Post, R. M. Intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. Life Sci. 26:1275–1282; 1980.
27. Racine, R. Kindling: the first decade. J. Neurosurg. 3:234–252; 1978.
28. Ticku, M. J.; Maksay, G. Convulsant/depressant site of action at the allosteric benzodiazepine-GABA receptor-ionophore complex. Life Sci. 33:2363–2375; 1983.
29. Vosu, H.; Wise, R. A. Cholinergic seizure kindling in the rat: comparison of caudate, amygdala and hippocampus. Behav. Biol. 13: 491–495; 1975.
30. Wood, J. D.; Davies, M. Regulation of the γ-aminobutyric $acid_A$ receptor by γ-aminobutyric acid level within the postsynaptic cell. J. Neurochem. 53:1648–1651; 1989.
31. Yonekawa, W. D.; Kupferberg, H. J.; Woodbury, D. M. Relationship between pentylenetetrazol-induced seizures and brain pentylenetetrazol levels in mice. J. Pharmacol. Exp. Ther. 214:589–593; 1980.