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The effects of drugs on barbiturate withdrawal convulsions in the rat

P. R. E. NORTON*

School of Pharmacy, Nottingham University, Nottingham, U.K.

The effects of drugs on barbitone withdrawal convulsions in rats have been examined. Morphine and mebanazine had no effect on audiogenically induced barbiturate withdrawal seizures. Alcohol, although suppressing the seizures, did not maintain drug dependence. Chlorpromazine prolonged the recovery period after the induction of the convulsions. Meprobamate, chlordiazepoxide and primidone substituted for the barbiturate and maintained drug dependence. 5-Hydroxytryptamine, when administered intraventricularly, tryptophan, α-methyl-*p*-tyrosine and ethosuximide reduced the severity of the withdrawal seizures. Reserpine and *p*-chlorophenylalanine greatly increased the severity of the seizures. Anxiolytic sedatives substituted for barbitone in dependent animals, other drugs studied affected barbiturate withdrawal convulsions in a way similar to other convulsive processes.

Crossland & Leonard (1963) have shown that rats can become physically dependent on barbiturates. The characteristics of the barbiturate withdrawal syndrome are similar to those in other animals and man (Turnbull, 1966). The withdrawal syndrome is characterized by a loss of body weight and a susceptibility to sound-induced convulsions; spontaneous convulsions are also sometimes seen. The effect of some centrally active drugs on the barbiturate withdrawal convulsions has been assessed in the hope that some indication could be obtained of the nature of the central nervous system changes induced by barbiturate dependence.

EXPERIMENTAL

Young adult female Wistar rats, not susceptible to audiogenic seizures, were used. Barbitone dependence was induced according to the method of Crossland & Leonard (1963) and Leonard (1967). In this method barbitone is dissolved in the drinking water in increasing concentration so that rats receive 400 mg/kg after 4 weeks. The taste of the barbitone is disguised with saccharin. The animals are dependent on barbitone after 5 weeks. Groups of five dependent rats were used for both experimental and control tests. Morphine and chlorpromazine were given subcutaneously, 5-hydroxytryptamine (5-HT) was given intraventricularly; the other drugs were administered by stomach tube as 2 ml of a suspension in a 5% mucilage of compound tragacanth powder B.P. Dosing was normally twice daily. Rats not receiving the drug served as controls and were always given the test vehicle. Miniature intraventricular cannulae were prepared (Norton, 1968) for the administration of 5-HT from 18–24 h after barbiturate withdrawal in a total dose of 140 μg, the last dose (40 μg) being given 15 min before the animals were tested for audiogenic seizures. In those experiments made to assess whether the drug would substitute for the

* Present address: B.D.H. Research Ltd., Godalming, Surrey, U.K.

barbiturate and maintain drug dependence, the drug was administered for about 5 days. In the other experiments the drugs were administered for 2 days.

At the time of barbiturate withdrawal and on each subsequent day the animals were weighed and placed in an experimental chamber and subjected to an auditory stimulus (bell intensity 100 dB for 1 min) to determine their susceptibility to seizures. Four types of convulsion were distinguished, in descending order of severity these were: an extensor tonic spasm in both front and hind legs, an extensor tonic spasm in the front legs only, a front leg flexor tonic spasm and generalized clonic convulsive activity. Spontaneous convulsive activity was recorded and was considered more severe than the convulsions induced by a bell. The significance of the drug effect on the convulsions was tested by ranking the convulsions in the order of severity. Convulsions within any one of these groups were then ranked according to the time taken to induce them.

RESULTS

The effects of drugs on the audiogenically induced barbiturate withdrawal convulsions are presented in Table 1.

Table 1. *The effect of drugs on the barbiturate withdrawal convulsion*

Drug	Daily dose mg/kg	Effect on withdrawal convulsions	Effect on ceasing drug administration
Morphine	20	0	
Meprobamate	2000	−−	++
Chlordiazepoxide ..	200	−−	++
Ethanol	see text	−−	
Chlorpromazine ..	10	0	
Reserpine	4	++	
Primidone	50	−−	++
Ethosuximide	400	−	
p-Chlorophenylalanine	300	+	
5-Hydroxytryptamine ..	see text	−	
Tryptophan	2000	−	
Mebanazine	10	0	
	20	0	
α-methyl-*p*-tyrosine ..	100	−	

− significantly less severe convulsion ($P < 0{\cdot}05$).
−− significantly less severe convulsion ($P < 0{\cdot}01$)
+ significantly more severe convulsion ($P < 0{\cdot}05$)
++ significantly more severe convulsion ($P < 0{\cdot}01$).

Morphine did not affect the barbiturate withdrawal syndrome but meprobamate and chlordiazepoxide prevented any withdrawal seizures occurring. When these drugs were withheld a syndrome developed identical to that of barbiturate withdrawal. The syndrome when chlordiazepoxide was withheld did not appear until 3 days later. In additional experiments, meprobamate (1 g/kg daily for 5 days) was found to cause dependence in rats that had received barbitone previously, but chlordiazepoxide (200 mg/kg daily for 5 days) did not. Similar meprobamate administration to previously untreated rats did not induce dependence. Primidone suppressed the barbiturate withdrawal seizures. After 6 days administration primidone was withheld and the animals became susceptible to audiogenic seizures. However this substitution appeared to be partial since the weight loss normally seen at barbiturate withdrawal occurred under primidone and the animals lost no weight

when primidone was no longer given. Ethanol suppressed the seizures but only at a dose that kept the animals markedly sedated (approximately 4 ml of a 75% solution daily). This continued sedation resulted in the death of most of the animals after 6 days. Chlorpromazine did not significantly affect the extent of the convulsions but recovery was slower and one animal died. Reserpine potentiated the withdrawal seizures, all animals having front and back leg extensor tonic convulsions, whereas none of the animals not receiving reserpine had convulsions of this severity, this effect was greater the longer the animals received the drug. *p*-Chlorophenylalanine increased the severity of the convulsions, most animals exhibiting extensor tonic spasm of both front and hind legs as opposed to the untreated animals showing only flexor tonic spasm of front legs. Five days after barbiturate withdrawal, tonic convulsions were seen in all animals which had received *p*-chlorophenylalanine whereas withdrawn animals not receiving the drug exhibited no convulsions at this time. Additional experiments were made with this drug and it was found that it did not make untreated animals susceptible to audiogenic seizures. In addition *p*-chlorophenylalanine had an anticonvulsant action on the seizures caused by a convulsant barbiturate (5-(1,3-dimethylbutyl)-5-ethyl barbituric acid (DMBEB), 10 mg/kg) when given 24 h previously.

Intraventricularly administered 5-HT, tryptophan, α-methyl-*p*-tyrosine and ethosuximide reduced the severity of the barbiturate withdrawal convulsions to a small extent. In all these groups some overlap was seen in the severity of the convulsions and separation of drugged and non-drugged groups ($P < 0{\cdot}05$) occurred due to the somewhat longer time taken to induce the convulsions in the drugged animals. The monoamine oxidase inhibitor mebanazine did not have any effect on the withdrawal seizures.

DISCUSSION

Cross dependence exists between barbiturate dependence and that induced by other depressant drugs (Weiss, 1964; Essig, 1966). However the present work has shown that the non-specific depressant drug ethanol, was not able to maintain drug dependence; this agrees with clinical observations (Fraser, Wikler & others, 1957). Depressants with a more specific action, meprobamate and chlordiazepoxide, substituted for the barbiturate and maintained drug dependence. Of the anticonvulsant drugs used, primidone suppressed the barbiturate withdrawal syndrome and also partially substituted for the drug. Ethosuximide reduced the severity of the seizures. Turnbull (1966) previously noted that diphenylhydantoin could suppress the barbiturate withdrawal seizures in the rat. These drug effects confirm the grand mal nature of the withdrawal seizures.

The neocortex plays very little part in the genesis of the barbiturate withdrawal seizure (Essig, 1962; Sharpless & Jaffe, 1966) and it has been concluded that the seizure arises subcortically (Essig & Flanary, 1961). A more specific effect than mere neuronal rebound hyperexcitability (Wikler, Fraser & others, 1955; Jaffe & Sharpless, 1965) is therefore likely and many general theories of drug dependence involving putative central synaptic transmitters have been proposed (Crossland, 1957; Collier, 1966). However Turnbull (1966) studied the whole brain concentrations of acetylcholine, γ-aminobutyric acid, noradrenaline, dopamine, 5-HT and histamine in barbiturate-dependent and withdrawn rats and concluded that his experiments provided no support for the hypothesis that barbiturate withdrawal convulsions in

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the rat are caused by a dearrangement of any of the transmitter substances investigated.

Substances considered to have reasonably specific effects on the synaptic transmitters 5-HT and noradrenaline, such as reserpine, tryptophan (Paasonen & Giarman, 1958), *p*-chlorophenylalanine (Koe & Weissman, 1968) and α-methyl-*p*-tyrosine (Spector, Sjoerdsma & Udenfriend, 1965), affected the withdrawal convulsions. Particularly striking was the increased severity of the barbiturate withdrawal seizures when reserpine or *p*-chlorophenylalanine were administered; both substances cause a decrease in whole brain content of 5-HT. Reserpine potentiates other forms of convulsions (Jones & Roberts, 1968), and *p*-chlorophenylalanine potentiates electroshock convulsions (Koe & Weissman, 1968) and therefore specificity of effect of these substances on the withdrawal syndrome is unlikely. It appears that the convulsions arising from barbiturate withdrawal are affected by drugs in a way similar to other convulsive processes.

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