Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, Nos. 2/3, pp. 249–253, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00372-6

A Study of the *N*-Methyl-D-Aspartate Antagonistic Properties of Anticholinergic Drugs[1]

JOHN H. McDONOUGH, JR.[2] AND TSUNG-MING SHIH

Biochemical Pharmacology Branch, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD 21010-5425

Received 5 July 1994

McDONOUGH JR., J. H. AND T.-M. SHIH. *A study of the* N-*methyl*-D-*aspartate antagonistic properties of anticholinergic drugs.* PHARMACOL BIOCHEM BEHAV. **51**(2/3) 249–253, 1995.—Drugs that act at the *N*-methyl-D-aspartate (NMDA) receptor complex have the ability to terminate nerve agent-induced seizures and modulate the neuropathologic consequences of agent exposure. Drugs with mixed anticholinergic and anti-NMDA properties potentially provide an ideal class of compounds for development as anticonvulsant treatments for nerve agent casualties. The present experiment evaluated the potential NMDA antagonist activity of 11 anticholinergic drugs by determining whether pretreatment with the compound was capable of protecting mice from the lethal effects of NMDA. The following anticholinergic drugs antagonized NMDA lethality and are ranked according to their potency: mecamylamine > procyclidine = benactyzine > biperiden > trihexyphenidyl. The anticholinergics atropine, aprophen, azaprophen, benztropine, 3-quinuclidinyl benzilate (QNB), and scopolamine failed to show NMDA antagonist properties. In addition, and unexpectedly, diazepam, ethanol, and pentobarbital were also shown to be capable of antagonizing NMDA lethality over a certain range of doses. The advantages and limitations of using antagonism of NMDA lethality in mice as a bioassay for determining the NMDA antagonist properties of drugs are also discussed.

Mouse *N*-methyl-D-aspartate Lethality Anticholinergic drug *N*-methyl-D-aspartate antagonists Anti-Parkinsonian drugs

CENTRALLY mediated seizures are one of the toxic signs that occur following poisoning with organophosphorus (OP) anticholinesterase nerve agents such as the compound soman (pinacolyl methylphosphonofluoridate) (4,6,15,16,19). Nerve agent-induced seizures are thought to involve both cholinergic and excitatory amino acid (EAA) processes (9,17,25). The initiation and early stages of the seizure appear to be controlled by cholinergic hyperactivity. Evidence supports this contention: At seizure onset the most notable neurochemical changes in brain involve inhibition of cholinesterase and a marked increase in brain acetylcholine (9,23); pretreatment (3) or early therapeutic treatment (17) with anticholinergic drugs will, respectively, block or terminate ongoing soman-induced seizures. However, if the seizure is allowed to progress unchecked, the seizure process per se, via excessive neuronal depolarization, results in a high release of the EAA transmitter glutamate that activates the *N*-methyl-D-aspartate (NMDA) system (9–12), which can then maintain seizure activity independent of the initial cholinergic excitation. Evidence in support of this hypothesis is that anticholinergic drugs such as scopolamine and atropine rapidly lose effectiveness as anticonvulsants the longer treatment is delayed after seizure onset. Eventually, the seizures become totally refractory to control with scopolamine if treatment is delayed for 40

[1] The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, proposed by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, DHHA, National Institute of Health Publication 85-23, 1985, and the Animal Welfare Act of 1966, as amended. The opinions or assertions contained herein are the private views of the authors, and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

[2] Requests for reprints should be addressed to Commander, US Army Medical Research Institute of Chemical Defense, Attn: MCMR-UV-PA (Dr. McDonough), Aberdeen Proving Ground, MD 21010-5425.

min after seizure onset (17). In contrast, NMDA antagonists [e.g., MK-801, *N*-(1-[2-thienyl] cyclohexyl)-piperidine (TCP)] are capable of terminating soman-induced seizures even if treatment is delayed 40 min after seizure onset (1,17,26). However, in nerve agent-intoxicated subjects these noncompetitive NMDA antagonists exert an immediate and profound respiratory depression that is rapidly lethal unless they are given in conjunction with an anticholinergic drug (17,24).

Several anticholinergic compounds (e.g., benactyzine, biperiden, procyclidine, and trihexyphenidyl) have been identified as being capable of terminating nerve agent seizures even at a long treatment delay when scopolamine is not effective (17,22; unpublished data). Other research has shown that three of these drugs (biperiden, procyclidine, and trihexyphenidyl) are capable of blocking the toxic effects of NMDA in the isolated chick retina preparation, indicating that they possess NMDA antagonist activity as well as have anticholinergic properties (20). Compounds with mixed anticholinergic and anti-NMDA activity potentially possess the ideal pharmacologic properties for treatment of nerve agent seizures, especially at long treatment delays. Thus far, only five anticholinergic antiparkinsonian drugs (procyclidine, ethopropazine, trihexyphenidyl, biperiden, and diphenhydramine) and the antinicotinic drug mecamylamine have been shown to have NMDA antagonist properties using the isolated chick retina preparation (20). The purpose of the present study was to expand on these initial findings and to test a series of anticholinergic drugs for NMDA antagonist activity using an in vivo bioassay sensitive to drugs with NMDA antagonist properties.

From the literature, the most reproducible and straightforward test of anti-NMDA activity in an in vivo model appeared to be the antagonism of NMDA-induced lethality (13,14). Although some investigators have used antagonism of NMDA-induced convulsions as an end point to evaluate potential anti-NMDA activity (8,21), Leander et al. (13) stated, "During the course of our studies, lethality proved to be the only pharmacological end-point that was most reliably produced by administration of NMDA and was blocked by phencyclidine-like drugs and specific NMDA-defined receptor antagonists, but not by other CNS drugs" (13, p. 116). For these reasons, antagonism of NMDA-induced lethality was used in this study as a bioassay to determine potential NMDA antagonist activity of a limited series of anticholinergic drugs.

METHOD

Subjects

Three hundred twenty-five CD-1 male mice (Charles River Labs, Wilmington, MA), weighing 20–30 g, served as subjects. The animals were group-housed until the day of the experiment. On the day of the experiment animals were placed in individual cages that allowed continuous observation and were kept in these cages for the next 24 h. Animals were kept in temperature (21 ± 2°C) and humidity (50 ± 10%) controlled animal quarters, and maintained on a 12 L : 12 D full-spectrum lighting cycle with lights on at 0600 h. Laboratory rodent chow and tapwater were freely available.

Drugs

Eleven anticholinergic drugs were tested: aprophen, atropine, azaprophen, benactyzine, benztropine, biperiden, mecamylamine, procyclidine, 3-quinuclidinyl benzilate (QNB), scopolamine, and trihexyphenidyl. All of these compounds, with the exception of QNB, have been shown to be effective in blocking or antagonizing nerve agent-induced convulsions or seizures (3,17,22). Two nonanticholinergic NMDA antagonists (MK-801 and ketamine) were tested as positive controls. The benzodiazepine diazepam and the barbiturate phenobarbital had been reported to be ineffective in this test (13), so diazepam and the barbiturate pentobarbital were tested as negative controls.

The drugs, their source, and the starting dose of each drug (in parentheses) are given subsequently. Aprophen HCl (0.1 mg/kg) and azaprophen HCl (0.1 mg/kg) were obtained from the Department of Experimental Therapeutics, Walter Reed Army Institute of Research. QNB (0.05 mg/kg) was obtained from the Drug Assessment Division of this Institute. Atropine SO_4 (0.5 mg/kg), benactyzine HCl (0.1 mg/kg), benztropine mesylate (0.1 mg/kg), biperiden HCl (0.1 mg/kg), mecamylamine HCl (0.1 mg/kg), procyclidine HCl (0.1 mg/kg), and trihexyphenidyl HCl (0.1 mg/kg) were obtained from Sigma (St. Louis, MO). Diazepam (0.2 mg/kg) was obtained from Hoffmann-LaRoche (Nutley, NJ). MK-801 (0.05 mg/kg) and NMDA were obtained from Research Biochemicals, Inc. (Natick, MA). Ketamine (4.0 mg/kg) was obtained from Aveco Co., Inc. (Fort Dodge, IO), and sodium pentobarbital (20 mg/kg) was obtained from Anpro Pharmaceutical (Arcadia, CA).

Most test compounds were prepared as stock solutions of 1, 10, or 100 mg/ml and maintained under refrigeration. The following were exceptions to this: diazepam, 5 mg/ml stock; and pentobarbital, 65 mg/ml stock. Absolute ethanol served as the diluent for the stock solution of QNB. Working solutions were prepared on the day of the experiment from these stocks. A vehicle solution consisting of 40% propylene glycol, 10% ethanol, 1.5% benzyl alcohol, and 48.5% sterile water served as the diluent for biperiden, diazepam, pentobarbital, and trihexyphenidyl. Saline (0.9%) served as the diluent for all other drugs. Drug solutions were prepared to deliver 1 ml/100 g body wt.

Procedures

The mice were weighed and placed in individual cages. Test drugs were administered subcutaneously (SC) 30 min before intraperitoneal (IP) injection of NMDA [the one exception was ketamine, which was given SC 15 min before NMDA because of its rapid time course of effect (13)]. Lethality was checked every 5 min for 30 min and again at 1, 2, 4, and 24 h after NMDA challenge. Animals that survived 24 h were euthanized with CO_2.

Determination of NMDA toxicity. The reported LD_{99} of NMDA given by IP injection in CF-1 male mice is 200 mg/kg (13). Using five groups of five mice each, this LD99 was verified for the CD-1 males used in this study. It was determined that 249 mg/kg NMDA was a better estimate of the LD99 (see RESULTS) under the conditions used here. Therefore, 250 mg/kg NMDA was used as the fixed challenge dose in the study.

Test of anticholinergic drugs. The up-down method (5) was used with the test drugs to establish an estimated ED_{50} for antagonism of NMDA-induced lethality. In using the up-down method, a starting dose of each drug was chosen, and a series of doses, separated by a constant 0.3-log dose interval, both above and below this starting dose, was also determined. In practice, the starting dose of the drug was tested; if lethality was antagonized in the first test animal, the next lower dose was tested in the next animal; if lethality was not antagonized, the next higher dose was tested in the next animal. In general each successive animal was tested at the dose level immediately below or above the dose level of the previous test, according

to whether lethality was antagonized or not on the previous test.

Statistical Analysis

The LD_{99} of NMDA was established using standard probit analysis (2). ED_{50}s for antagonism of NMDA-induced lethality were determined using standard calculations outlined for the up-down procedure (5). Where applicable, the data also were subjected to probit analysis (2).

RESULTS

The toxicity of NMDA (IP) in CD-1 male mice was determined to be LD_{50} = 196.44 mg/kg (180.93 – 213.03 mg/kg = 95% confidence limits); LD_{99} = 249.36 mg/kg (224.82 – 361.81 mg/kg = 95% confidence limits). The behavioral responses of the mice to increasing doses of 158–251 mg/kg NMDA consisted of hyperactivity, scratching, jumping, tail biting, "barrel rolling," and opisthotonos-type convulsions. Death typically occurred in conjunction with a severe convulsive episode. Signs of intoxication began 5–10 min after injection, were typically most severe 20–30 min after injection, and began to wane after 45–60 min; > 90% of the deaths occurred within 45 min after NMDA injection and < 1% occurred longer than 4 h after NMDA.

Five of the anticholinergic compounds failed to show any ability to antagonize the lethal effects of NMDA. Among the 10 drugs that consistently showed antagonism were five anticholinergic drugs, the two known NMDA antagonists, a barbiturate, a benzodiazepine, and QNB/ethanol. Table 1 presents the ED_{50} of each effective compound as calculated by the up-down estimate method (5) and rank orders their potency on a milligram per kilogram basis; the molecular weight ED_{50} is also provided. The ED_{50}s as calculated by the probit method (2) showed good agreement with the ED_{50} estimates calculated with the up-down method (5). However, confidence limits could not always be obtained with the probit method because of small and/or variable numbers of subjects in the dose groups within the effective dose range of some of the compounds.

Atropine, aprophen, azaprophen, benztropine, and scopolamine failed to show any ability to protect animals against the lethal effects of NMDA. With all five compounds, ascending doses were tested from 0.1 mg/kg up to doses of four of the drugs that were themselves lethal before the NMDA challenge could be given (atropine, 256 mg/kg; azaprophen and benztropine, 409.6 mg/kg; scopolamine, 819.2 mg/kg). The highest dose of aprophen tested was 409.6 mg/kg, and although this dose was not lethal it also failed to protect against the lethal effects of NMDA.

The five anticholinergics capable of antagonizing NMDA-induced lethality, and their order of potency, were: mecamylamine, procyclidine, benactyzine, biperiden, and trihexyphenidyl. Both the specific NMDA antagonists ketamine and MK-801 were effective in blocking the lethal effects of NMDA. The calculated ED_{50}s (Table 1) were only slightly less than those reported in the literature [MK-801, 0.32 mg/kg; ketamine, 40 mg/kg; (13)].

Both diazepam and pentobarbital were effective in antagonizing NMDA-induced lethality within limited dose ranges. For diazepam, only doses 0.1–0.2 mg/kg were effective in antagonizing lethality; doses ≥ 0.4 mg/kg were ineffective, as were doses ≤ 0.05 mg/kg. With pentobarbital, doses 20–80 mg/kg showed the ability to antagonize NMDA lethality, even though at the 40- and 80-mg/kg doses the animals were in an anesthetic-like state when NMDA was given and throughout most of the intoxication.

3-Quinuclidinyl benzilate effectively antagonized NMDA induced lethality at an ED_{50} of 2.15 mg/kg. However, it was noted that the animals were markedly sedated at this dose. Because ethanol was the vehicle for the stock solution of QNB, administration of 2.15 mg/kg QNB also resulted in the administration of a pharmacologically significant dose of ethanol (2.02 g/kg). Further tests done with the ethanol vehicle alone showed that ethanol (ED_{50} = 1.56 g/kg) itself protected against NMDA in the same dose range as calculated for QNB. Therefore, it is unlikely that QNB by itself exerted any NMDA antagonism.

TABLE 1

ED_{50} FOR ANTAGONISM OF NMDA-INDUCED LETHALITY BY ANTICHOLINERGIC AND OTHER DRUGS

Drug	ED_{50} mg/kg (SEM)	μmol/kg
Diazepam	0.1 (0.07–0.12)	0.4
MK-801	0.1 (0.09–0.14)	0.5
Mecamylamine	12.0 (8.8–16.4)	59.0
Procyclidine	21.4 (16.5–27.8)	66.2
Ketamine	26.4 (20.5–34.0)	98.4
Benactyzine	27.5 (20.5–37.0)	75.6
Pentobarbital	29.9 (22.8–39.2)	120.4
Biperiden	86.1 (61.0–121.6)	247.5
Trihexyphenidyl	305.5 (220.8–422.7)	904.0
Ethanol	1560.0 (1081–2256)	33,870.2
QNB/Ethanol*	2.2 (1.6–2.9)/2021.0 (1532–2679)	43,879.3

* ED_{50} of both the QNB and the ethanol content of the QNB drug solution.

DISCUSSION

The results of the present experiment showed that a number of anticholinergic drugs antagonized NMDA-induced lethality. However, the results also showed that a number of drugs originally included in the study as negative controls were capable of antagonizing NMDA-induced lethality over a restricted dose range.

Atropine, aprophen, azaprophen, benztropine, and scopolamine were not capable of blocking the lethal effects of NMDA. At least for atropine and scopolamine, this agrees with the findings reported by Olney et al. (20), that these drugs do not block the toxic effects of NMDA on the in vitro isolated chick retina preparation. This further substantiates the conclusion that these compounds probably do not have NMDA antagonist properties, as neither drug could terminate nerve agent-induced seizures at long delays after seizure onset (17). Based on the present findings, it is suggested that aprophen, azaprophen, and benztropine would also display limited or no effectiveness against nerve agent-induced seizures if treatment were delayed > 20 min. It should be noted that all these drugs are potent antagonists of nerve agent convulsions when given before seizure onset (3). QNB should also be included in this group of anticholinergic drugs devoid of NMDA antagonist activity in this test. The results clearly showed the protective effects of QNB to be coincident with, and equivalent to, the administration of pharmacologically significant doses of ethanol that served as the stock diluent for QNB.

The anticholinergic drugs mecamylamine, procyclidine, be-

nactyzine, biperiden, and trihexyphenidyl, in that order of potency, were all capable of antagonizing NMDA-induced lethality. With both biperiden and trihexyphenidyl, the effective dose range was also coincident with the upper limits of solubility of each drug. The rank order of potency in the present experiment was substantially different from that reported by Olney et al. (20) for antagonism of the toxic effects of NMDA in vitro on the isolated chick retina preparation. In that study (20), the order of potency of compounds was: MK-801, ketamine, procyclidine, mecamylamine, trihexyphenidyl, and biperiden (benactyzine was not studied). In the present study, the rank orders were: MK-801, mecamylamine, procyclidine, ketamine, benactyzine, biperiden, and trihexyphenidyl. It can be concluded that although the isolated chick retina preparation can identify compounds with NMDA antagonist properties, it does not accurately predict their in vivo efficacy in another bioassay directed at identifying the same pharmacologic properties. This further reinforces the conclusion of McQuaid et al. (18), that although in vitro assays are able to identify intrinsic activity at NMDA receptors, they do not take into account factors such as absorption, distribution, and metabolism, which can affect drug action in vivo, and thus tend to overestimate the potential in vivo activity of certain drugs. In this study mecamylamine, procyclidine, and benactyzine displayed potencies at least equivalent to that of the well-recognized NMDA antagonist ketamine, whereas in vitro studies consistently rank ketamine as significantly more potent than these compounds (18,20). Finally, it should be noted that the present results support the speculation that benactyzine, an anticholinergic capable of terminating nerve agent seizures even when treatment is delayed, may possess anti-NMDA properties (17).

Previous work by Leander et al. (13) showed that diazepam and phenobarbital were ineffective in antagonizing NMDA-induced lethality in mice. For this reason, diazepam and pentobarbital, a barbiturate similar to phenobarbital, were used in the present study as negative controls. Surprisingly, however, both compounds showed an ability to protect against NMDA over a restricted range of doses (diazepam: 0.1–0.2 mg/kg; pentobarbital: 20–80 mg/kg). Doses of diazepam $\leq$ 0.05 or $\geq$ 0.4 mg/kg were consistently ineffective; doses of pentobarbital $\leq$ 10 mg/kg were not effective and the next scheduled higher dose (i.e., 160 mg/kg) would have been lethal by itself. In reviewing the Leander et al. (13) study to try and reconcile these discrepant findings, aside from the different mouse strains used (CD-1 vs. CF-1), we noted that they reported only on the highest dose of drug tested. For diazepam this was 20 mg/kg, a dose two orders of magnitude greater than the dose found to be protective in the present study. For phenobarbital the dose was 80 mg/kg. The present findings suggest that moderate doses of drugs that depress behavior and have anticonvulsant properties (diazepam, pentobarbital, and ethanol) can provide some limited protection against NMDA lethality under these conditions. Most likely the protective effect of these drugs is pharmacologically nonspecific, especially in the case of diazepam, as here higher doses of the presumed antagonist (diazepam) actually lost effectiveness.

In turn, these findings call into question whether antagonism of NMDA lethality can be considered a specific in vivo bioassay for compounds that act as competitive or noncompetitive NMDA receptor antagonists (13). Lethality due to NMDA intoxication is no doubt a result of toxic activity at multiple organ systems (e.g., seizures, respiratory difficulties, cardiac effects), and an indirect moderation of any one of these effects may be sufficient to antagonize a lethal outcome. Likewise, there are other sites on the NMDA receptor complex that drugs of different classes might act on to bring about a diminished effect from NMDA challenge. Most recently, it was reported that biperiden, procyclidine, and trihexyphenidyl, as well as some other anticholinergics used in the treatment of Parkinson's disease, can inhibit NMDA-evoked release of acetylcholine from caudate nucleus slices and, at least biperiden, also could displace specifically bound [^{3}H]MK-801 from caudate nucleus membranes (7). The authors concluded that these anticholinergics act as uncompetitive antagonists at the NMDA receptor and bind to the the receptor-linked ion channel, but not to the MK-801/phencyclidine binding site.

In summary, a number of anticholinergic drugs were tested for their ability to antagonize a lethal challenge of NMDA in mice. Mecamylamine, procyclidine, benactyzine, biperiden, and trihexyphenidyl, in that order of potency, were capable of blocking the lethal effects of NMDA, and are thus inferred to have some NMDA antagonist properties. Some of these drugs (mecamylamine, procyclindine, and benactyzine) had potencies equivalent to or greater than the NMDA antagonist ketamine. However, the previously claimed specificity of this bioassay could not be confirmed because diazepam, ethanol, and pentobarbital also proved capable, within restricted dose ranges, of blocking the lethal effect of NMDA.

ACKNOWLEDGEMENTS

The authors acknowledge the technical assistance of Mr. Thomas A. Koviak. Dr. McDonough was a National Research Council Senior Associate during the perfomance of this work.

REFERENCES

1. Blanchet, G.; Carpentier, P.; Lallement, G.; Tarricone, A.; Sentenac, H.; Kamenka, J.-M. Anticonvulsant effect of N-[1-(2-thienyl) cyclohexyl]-piperidine (TCP) in soman poisoning. In: Kamenka, J.-M.; Domino, E. F., eds. Multiple sigma and PCP receptor ligands: Mechanisms for neuromodulation and protection. Ann Arbor, MI: NPP Books; 1992:831–840.
2. Bliss, C. I. The statistics of bioassay with special reference to the vitamins. In: Vitamin methods, vol. II, New York: Academic Press; 1952.
3. Capacio, B. R.; Shih, T.-M. Anticonvulsant action of anticholinergic drugs in soman poisoning. Epilepsia 32:604–615; 1991.
4. Clement, J. G.; Lee, M. J. Soman-induced convulsions: Significance of changes in levels of blood electrolytes, gases, glucose and insulin. Toxicol. Appl. Pharmacol. 55:203–204; 1980.
5. Dixon, W. J.; Massey, F. J. Introduction to statistical analysis. New York: McGraw-Hill; 1981:426–441.
6. Glenn, J. F.; Hinman, D. J.; McMaster, S. B. Electroencephalographic correlates of nerve agent poisoning. In: Dun, N. J.; Perlman, R. L., eds. Neurobiology of acetylcholine. New York: Plenum Press; 1987:503–534.
7. Jackisch, R.; Kruchen, A.; Ruzgar, M.; Hertting, G. NMDA antagonistic properties of budipine and other antimuscarinic drugs used in Parkinson's disease. Can. J. Physiol. Pharmacol. 72(Suppl 1):333; 1994.
8. Johnson, L. C.; DeNoble, V. J. *N*-Methyl-d-aspartic acid (NMDA) induced convulsions in mice: An *in vivo* model to identify NMDA antagonists. Neurosci. Abstr. 14:98.20; 1988.
9. Lallement, G.; Carpentier, P.; Collet, A.; Baubichon, D.; Pernot-Marino, I.; Blanchet, G. Extracellular acetylcholine changes in rat limbic structures during soman-induced seizures. Neurotoxicology 13:557–568; 1992.
10. Lallement, G.; Carpentier, P.; Collet, A.; Pernot-Marino, I.;

Baubichon, D.; Blanchet, G. Effects of soman-induced seizures on different extracellular amino acid levels and on glutamate uptake in rat hippocampus. Brain Res. 563:234–240; 1991.
11. Lallement, G.; Carpentier, P.; Collet, A.; Pernot-Marino, I.; Baubichon, D.; Sentenac-Romanou, H.; Blanchet, G. Involvement of the glutamatergic system in the amygdala during soman-induced seizures: Comparison with the hippocampus. Compte Rendus Acad. Sci. Paris 313(Serie III):421–426; 1991.
12. Lallement, G.; Carpentier, P.; Pernot-Marino, I.; Baubichon, D.; Collet, A.; Blanchet, G. Involvement of the different rat hippocampal glutamatergic receptors in development of seizures induced by soman: An autoradiographic study. Neurotoxicology 12:655–664; 1991.
13. Leander, J. D.; Lawson, R. R.; Ornstein, P. L.; Zimmerman, D. M. *N*-Methyl-d-aspartic acid-induced lethality in mice: Selective antagonism by phencyclidine-like drugs. Brain Res. 448:115–120; 1988.
14. Leander, J. D.; Rathbun, R. C.; Zimmerman, D. M. Anticonvulsant effects of phencyclidine-like drugs: relation to *N*-methyl-d-aspartic acid antagonism. Brain Res. 454:368–372; 1988.
15. Lipp, J. A. Cerebral electrical activity following soman administration. Arch. Int. Pharmacodyn. 175:161–169; 1968.
16. Lipp, J. A. Effect of diazepam upon soman-induced seizure activity and convulsions. Electroencephalogr. Clin. Neurophysiol. 32: 557–560; 1972.
17. McDonough, J. H.; Shih, T.-M. Pharmacological modulation of soman-induced seizures. Neurosci. Biobehav. Rev. 17:203–215; 1993.
18. McQuaid, L. A.; Leander, J. D.; Mendelsohn, L. G.; Smith, E. C. R.; Lawson, R. R.; Mason, N. R. Inhibition of [^{3}H]-MK-801 binding and protection against NMDA-induced lethality in mice by a series of imipramine analogs. Res. Commun. Chem. Pathol. Pharmacol. 77:171–178; 1992.
19. Misulis, K. E.; Clinton, M. E.; Dettbarn, W.-D.; Gupta, R. C. Differences in central and peripheral neural actions between soman and diisopropyl fluorophosphate organophosphorus inhibitors of acetylcholinesterase. Toxicol. Appl. Pharmacol. 89:391–398; 1987.
20. Olney, J. W.; Price, M. T.; Labruyere, J.; Salles, K. S.; Frierdich, G.; Mueller, M.; Silverman, E. Anti-Parkinsonian agents are phencyclidine agonists and *N*-methyl-aspartate antagonists. Eur. J. Pharmacol. 142:319–320; 1987.
21. Pontecorvo, M. J.; Karbon, E. W.; Goode, S.; Clissold, D. B.; Borosky, S. A.; Patch, R. J.; Ferkany, J. W. Possible cerebroprotective and in vivo NMDA antagonist activities of sigma agents. Brain Res. Bull. 26:461–465; 1991.
22. Price, M. T.; Stewart, G. R.; Olney, J. W. Procyclidine protects against soman neurotoxicity, even when administered after onset of convulsions. Soc. Neurosci. Abstr. 15:1349; 1989.
23. Shih, T.-M. Time course effects of soman on acetylcholine and choline levels in six discrete areas of the rat brain. Psychopharmacology (Berlin) 78:170–175; 1982.
24. Shih, T.-M. Anticonvulsant effects of diazepam and MK-801 in soman poisoning. Epilepsy Res. 7:105–116; 1990.
25. Shih, T.-M.; Koviak, T. A.; Capacio, B. R. Anticonvulsants for poisoning by the organophosphorus compound soman: pharmacological mechanisms. Neurosci. Biobehav. Rev. 15:349–362; 1991.
26. Sparenborg, S.; Brennecke, L. H.; Braitman, D. J. Dizocilpine (MK-801) arrests status epilepticus and prevents brain damage induced by soman. Neuropharmacology 31:357–368; 1992.