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European Journal of Pharmacology 347 (1998) 51–56

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5-Hydroxytryptophan-induced myoclonus in guinea pigs: mediation through 5-$HT_{1/2}$ receptor subtypes

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Received 1 December 1997; accepted 27 January 1998

Abstract

In guinea pigs, myoclonus can be induced by 5-hydroxytryptamine (5-HT, serotonin) precursors and synthetic 5-HT receptor agonists, yet the receptor subtype specificity of this behavior is not fully delineated. Guinea pigs were pre-treated with carbidopa (50 mg) followed by one of eight 5-HT antagonists: (−)-*N*-*tert*-butyl-3-[4-(2-methoxyphenyl) piperazin-1-yl]-2-phenyl propionamide ((−)-WAY 100135) (5-HT_{1A}), *N*-[2-[4-(2-methoxypheny)-1-piperazinyl]-ethyl]-*N*-(2-pyridyl)-cyclohexancarboxamide (WAY 100635) (5-HT_{1A}), methiothepin mesylate (5-$HT_{1/2}$), mesulergine hydrochloride (5-$HT_{2A/2C}$), *N*[4-methoxy-3-(4-methyl-L-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadizol-3-yl) (GR 127935) (5-HT_{1D}), *trans*-4-[(3*Z*)3-(2-dimethylaminoethyl)oxyimino-3(2-fluorophenyl) propen-1-yl]phenol, hemifumarate (SR 46349) (5-HT_2), ondansetron hydrochloride (5-HT_3), and [1-[2-[methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl-5-fluoro-2-methoxy-1*H*-indole-3-carboylate (GR 125487) (5-HT_4). Thirty minutes later, they received 5-hydroxytryptophan (5-HTP) (75 mg/kg, sc) and myoclonic jumping rates were assessed every 10 min for 200 min by a blinded observer. Repeated measures analysis of variance of drug-induced antagonism of 5-HTP-induced myoclonus revealed a significant effect for the 5-HT receptor antagonists methiothepin mesylate, GR127935, and mesulergine hydrochloride compared to placebo, and each of these drugs inhibited 5-HTP-induced myoclonus in a dose-dependent fashion. Based on the receptor profiles of the three effective antagonists, 5-HTP-induced myoclonus is influenced by the 5-$HT_{1/2}$ receptor systems. The absence of a significant change with any other receptor subtype antagonist suggests that myoclonus is not related to diffuse activation of central serotonergic mechanisms. © 1998 Elsevier Science B.V.

Keywords: Myoclonus; (Guinea pig); 5-HT (5-hydroxytryptamine, serotonin); 5-Hydroxytryptophan

1. Introduction

Clinical observations and pharmacological studies suggest abnormalities in the serotonin (5-hydroxytryptamine, 5-HT) system in some forms of human myoclonus (Brissaud and Beauvais, 1969; Dyken and Kola, 1968; Solomon and Chutorian, 1968). Specifically, in post-hypoxic myoclonus (Lance–Adams syndrome) (Lance and Adams, 1963), multiple studies including cerebrospinal fluid analyses and clinical trials suggest a specific link to 5-HT pharmacology (Lhermitte et al., 1972; Thal et al., 1980).

In guinea pigs, generalized myoclonic jumping behavior can be induced by the subcutaneous injection of 5-hydroxytryptophan (5-HTP), the immediate precursor to 5-HT (Klawans et al., 1973). This behavior is abolished by the acute administration of methysergide, a non-specific serotonergic antagonist (Goetz and Klawans, 1974). Intracisternal injections of 5,7-dihydroxytryptamine or chronic treatment with non-specific 5-HT receptor antagonists induces supersensitivity to this myoclonic response (Klawans et al., 1975; Pranzatelli and Snodgrass, 1987).

In the last decade, numerous 5-HT receptor subtypes have been identified and are heterogeneously distributed throughout the nervous system (Gozlan et al., 1983; Hartig et al., 1996; Heuring and Peroutka, 1987; Hoyer et al., 1988, 1994; Leonhardt et al., 1989; Leysen et al., 1982; Peroutka, 1986). Pranzatelli et al. (1993b) demonstrated that the guinea pig brain stem contained all of the 5-HT_1 receptor binding sites, as well as agonist- and antagonist-labeled 5-HT_2 sites and 5-HT uptake/transporter sites. In this animal, serotonin receptor binding site density rank order is: 5-HT_{1D} > antagonist-labeled 5-HT_2 > 5-HT_{1A} and 5-HT_{2C} > 5-HT_{1E} > agonist-labeled 5-HT_2 (Pranzatelli et al., 1993b).

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In addition to 5-HTP induction, myoclonic jumping behavior can be induced by indole-containing 5-HT receptor agonists (Luscombe et al., 1982), as well as 5-MeODMT (Eison et al., 1993). Because these agents are not selective for specific receptor populations, a clear delineation of the receptors linked to myoclonic jumping behavior has not been possible, and no study has examined the effect of selective 5-HT receptor antagonists on myoclonic jumping behavior. To complement the agonist studies and further delineate receptor specificity, we have tested the effects of a series of 5-HT receptor antagonists on myoclonic jumping behavior.

Table 1
Drugs and doses used to assess antagonism of 5-HTP-induced myoclonic jumping behavior

Primary receptor system	Antagonist	Intraperitoneal
5-HT_{1A}	WAY 100135	2.0 mg/kg
5-HT_{1A}	WAY 100635	1.0 mg/kg
5-$HT_{1/2}$	methiothepin mesylate	5.0 mg/kg
5-$HT_{2A/2C}$	mesulergine hydrochloride	10.0 mg/kg
5-HT_{1D}	GR 127935	7.0 mg/kg
5-HT_2	SR 46349	5.0 mg/kg
5-HT_3	ondansetron	100.0 μg/kg
5-HT_4	GR 125487	6.0 mg/kg
Control	normal saline	
Vehicle	dimethyl sulfoxide	

2. Materials and methods

2.1. Animals

Adult, white, male, litter-mate guinea pigs (250–299 g) were obtained from Harlan Laboratory (Indianapolis, IN, USA) and housed two per cage in a temperature-controlled room (23°C) with a 12 h light and dark cycle for seven days of acclimatization. Food and water were provided ad libitum. On the day of testing, animals were removed to individual rating cages, and time 0 for all experiments (see below) was noon. All experimental procedures were approved by the Rush Medical College Institutional Animal Care and Use Committee.

2.2. Animal model and overall study design

The model is based on subcutaneous administration of 5-HTP (75 mg/kg) injected at time 0 with oral carbidopa 25 mg p.o. given at −4 h and −2 h. Within 20 min of injection, guinea pigs develop piloerection, increased defecation and extensive grooming behavior. Thirty minutes after injection, they predictably show discontinuous jerking movements of the head and neck, which progressively increase in intensity and frequency to involve the whole body at a regular rate. The peak frequency occurs between 60 and 90 min after injection, and normal behavior recurs after 200 min. For all experiments, rating assessments began at time +30 min, and continued at ten min intervals to time +230 min. All antagonist drugs were administered at time −30 min.

2.3. Drugs

5-Hydroxytryptophan was obtained from Sigma (St. Louis, MO, USA), and supersaturated in distilled water at a concentration of 40 mg/ml and gradually acidified with 4 N hydrochloric acid until in solution. (−)-*N*-*tert*-butyl-3-[4-(2-methoxyphenyl) piperazin-1-yl]-2-phenyl propionamde ((−)WAY 100135) and *N*-[2-[4-(2-methoxypheny)-1-piperazinyl]-ethyl]-*N*-(2-pyridyl)-cyclohexan-carboxamide (WAY 1000635) (Wyeth Laboratories, Maidenhead, UK), methiothepin mesylate (Research Biochemicals, Natick, MA, USA), mesulergine hydrochloride (Sandoz Pharmaceutical, Basel, Switzerland), and [1-[2-[methyl-sulphonyl)amino]ethyl]-4-piperidinyl]methyl-5-fluoro-2-methoxy-1*H*-indole-3-carboxylate (GR 125487) (Glaxo Pharmaceuticals, Hertforshire, UK) were mixed with water. Ondansetron hydrochloride (Glaxo) was mixed with water at 32 mg/ml at a pH of 4.3, and *N*[4-methoxy-3-(4-methyl-L-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadizol-3-yl) (GR 127935) (Glaxo) solutions were prepared by heating a dispersion in 40% water at 70°C, and then cooling. *Trans*-4-[(3*Z*)3-(2-dimethylaminoethyl)-oxyimino-3(2-fluorophenyl) propen-1-yl]phenol hemifumarate (SR 46349) (Sanofi, Montpelier, France) was solubilized in dimethyl sulfoxide (DMSO) and protected from light. Normal saline and DMSO were utilized for placebo injections when appropriate Table 1.

2.4. Behavioral studies

We assessed eight 5-HT receptor antagonists with differing activity at serotonergic receptor sub-types. Based on prior studies, we designed our protocol to test a high dose for each drug that maintained serotonergic receptor subtype specificity (see Lejeune et al., 1993; Routledge et al., 1993; Forster et al., 1995; Mundey et al., 1996; King et al., 1997 for the specific blockade of 5-HT_{1A} receptors by WAY-100135 and WAY-100635; see Bradley et al., 1986; Skarsfeldt et al., 1990; Pranzatelli et al., 1993a for the specific blockade of 5-$HT_{1/2}$ receptors by methiothepin; see King et al., 1989; Cesana et al., 1993; Bourson et al., 1996 for the specific blockade of 5-$HT_{2A/2C}$ receptors by mesulergine; see Hutson et al., 1995; Skingle et al., 1995 for the specific blockade of 5-HT_{1D} by GR127935; see Rinaldi-Carmona et al., 1992, 1993; Chaouloff et al., 1997 for the specific blockade of 5-HT_2 receptors by SR46349; see Costall et al., 1989; Forster and Dockray, 1990; Cooper et al., 1993 for the specific blockade of 5-HT_3 receptors by ondansetron; see Letty et al., 1997; Marchetti-Gauthier et al., 1997 for the specific blockade of 5-HT_4 receptors by GR125487).

Forty guinea pigs were weighed and randomly assigned to receive one of eight 5-HT antagonists, DMSO or normal saline. Timing of the experiment and injection schedule followed that outlined in Section 2.2. In order to determine which drugs lowered myoclonic jumping behavior by at least 50%, mean myoclonic jumping behavior values for the four animals that received normal saline were set at 100%. Comparisons of each 5-HT receptor antagonist were calculated against this value.

For all antagonists that inhibited myoclonic jumping behavior by at least 50% compared to placebo at the initial, receptor-specific dose, we performed dose-response experiments with six doses, graded decrementally from the dose used in the prior experiment to 5% of that dose. For drugs that did not inhibit myoclonic jumping behavior at the initial dose, we did not perform decremental dose-response studies because inhibition criteria had not been met in the prior experiment at the dose associated with receptor-specific blockade. Likewise, for these drugs, we did not perform incremental dose-response studies, because higher doses lacked 5-HT receptor sub-type specificity. For these experiments, four animals were weighed and randomly assigned to each drug dose or normal saline. Timing of the experiment and injection schedule followed, outlined in Section 2.2.

2.5. Rating system

All animals were tested pharmacologically and rated in a sound-proof room at the same time of day. Beginning 30 min after 5-HTP injection (60 min after 5-HT receptor antagonist administration), myoclonic jumping behavior was quantified by counting the number of jumps/min at 10-min intervals over the subsequent 200 min. Total myoclonic jumping behavior scores equaled the sum of the 20 separate interval scores (30, 40, 50, . . . , 200 min).

2.6. Sample size determination and data analysis

Sample size determinations were based on a priori power calculations. Data were based on a study that quantified changes in 5-HTP-induced myoclonic jumping behavior in guinea pigs, following the administration of dopaminergic agonists, by counting the jumps at 10-min intervals after 5-HTP injection (Weiner et al., 1979). Using those values as baseline estimates of myoclonic jumping behavior, a sample size of four animals was determined to be needed to detect a decrease of 50% when 5-HT antagonists were co-injected. This is based on an α of 0.05, and a 1-β (power) of 0.85. Data were analyzed using repeated measures analysis of variance (ANOVA) of drug-induced antagonism of 5-HTP-induced myoclonus, with post-hoc individual comparisons using Scheffe's method.

3. Results

When all antagonists administered at the single high doses were considered together in comparison to placebo, there was a significant drug-induced antagonism of 5-HTP myoclonic jumping behavior ($F[9,171] = 2.65$, $p < 0.0001$). Individual comparisons revealed significant reductions ($\geq 50\%$) compared with placebo for three drugs: methiothepin mesylate ($p = 0.007$), mesulergine hydrochloride ($p = 0.006$), and GR 127935 ($p = 0.007$) (Fig. 1). While the administration of SR 46349 reduced myoclonic jumping behavior by nearly 40% as compared to normal saline, this effect was not statistically significant ($p = 0.053$).

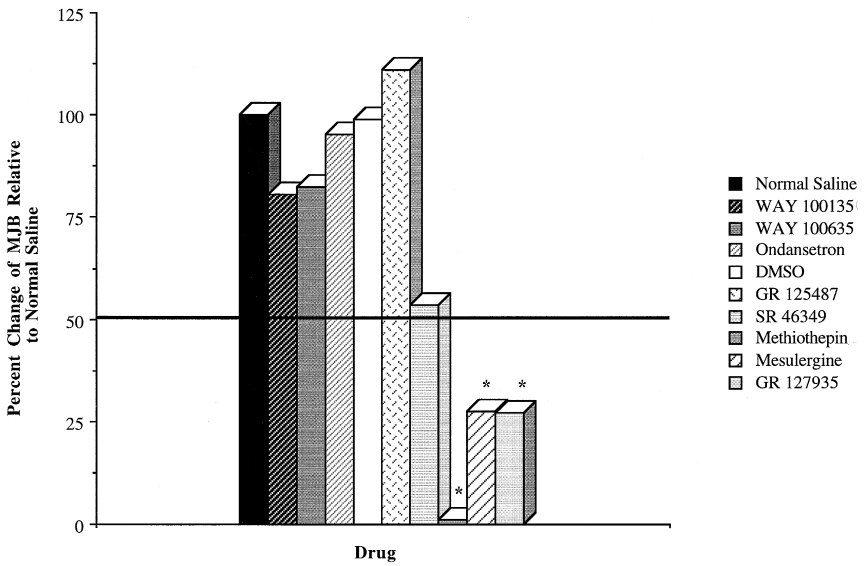

Fig. 1. Effects of eight 5-HT antagonists and dimethyl sulfoxide (DMSO) vs. normal saline on 5-hydroxytryptophan (5-HTP)-induced myoclonic jumping behavior.

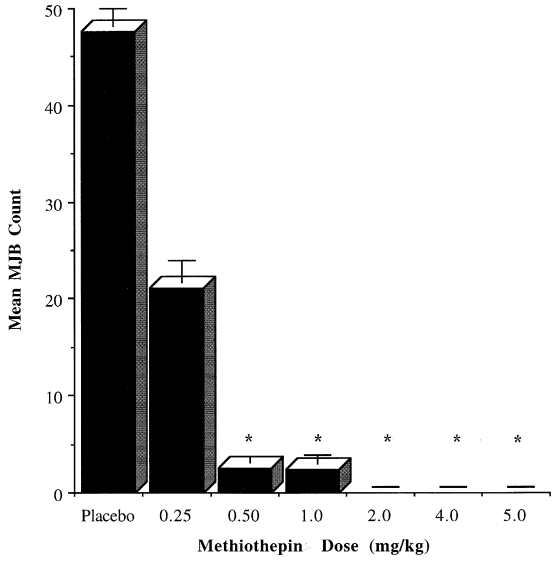

Fig. 2. Dose–response effects of methiothepin mesylate on 5-hydroxytryptophan (5-HTP)-induced myoclonic jumping behavior.

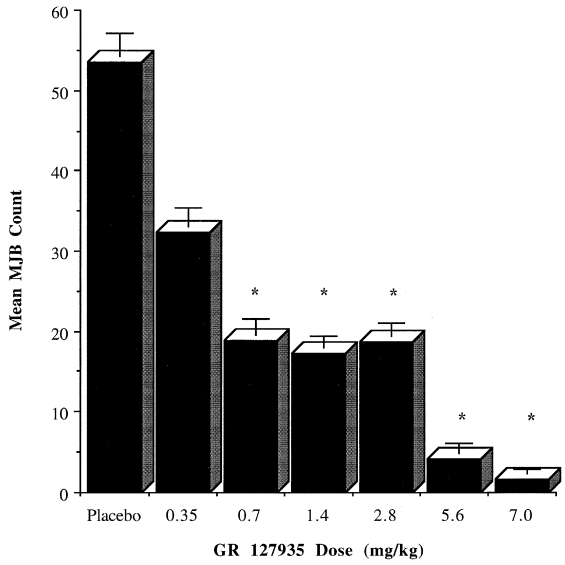

Fig. 4. Dose–response effects of GR 127935 on 5-hydroxytryptophan (5-HTP)-induced myoclonic jumping behavior.

With methiothepin mesylate, there was a significant effect of drug dose on myoclonic jumping behavior (main effect of dose), $F[6,323] = 29.54$, $p < 0.0001$. There was also a significant effect on myoclonic jumping behavior across time (main effect of time), $F[19,323] = 12.82$, $p < 0.0001$. The interaction between dose and time was also significant (dose × time), $F[114,323] = 5.33$, $p < 0.0001$. Post-hoc comparisons (Scheffe's analysis) indicated a significant difference in myoclonic jumping behavior between placebo and all doses (all p values < 0.003). Doses greater than or equal to 2.0 mg/kg completely abolished myoclonic jumping behavior (Fig. 2).

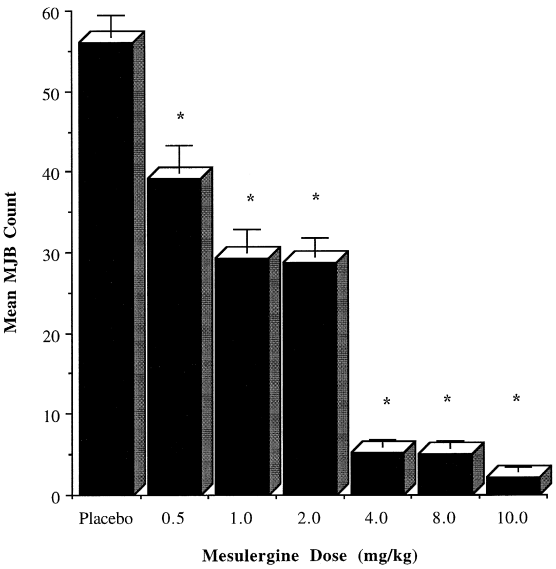

Fig. 3. Dose–response effects of mesulergine hydrochloride on 5-hydroxytryptophan (5-HTP)-induced myoclonic jumping behavior.

With mesulergine hydrochloride, there was a significant effect of drug dose on myoclonic jumping behavior (main effect of dose), $F[6,323] = 102.46$, $p < 0.0001$. There was also a significant effect on myoclonic jumping behavior across time (main effect of time), $F[19,323] = 122.04$, $p < 0.0001$. The interaction between dose and time was significant (dose × time), $F[114,323] = 20.16$, $p < 0.0001$. Post-hoc comparisons (Scheffe's analysis) revealed a significant difference in myoclonic jumping behavior between placebo and all doses (all p values < 0.003). No dose completely abolished myoclonic jumping behavior (Fig. 3).

With GR 127935, there was a significant effect of drug dose on myoclonic jumping behavior (main effect of dose), $F[6,323] = 16.57$, $p < 0.0001$. There was also a significant effect on myoclonic jumping behavior across time (main effect of time), $F[19,323] = 24.38$, $p < 0.0001$. The interaction between dose and time was significant (dose × time), $F[114,323] = 3.55$, $p < 0.0001$. Post-hoc comparisons (Scheffe's analysis) revealed no significant difference in myoclonic jumping behavior using 0.35 mg/kg ($p = 0.11$), but all other doses produced significant differences in myoclonic jumping behavior (all p values < 0.004). No dose completely abolished myoclonic jumping behavior (Fig. 4).

4. Discussion

Myoclonic jumping behavior is a well-established animal model of generalized, non-epileptic myoclonus (Klawans et al., 1973). Myoclonic jumping behavior relates pharmacologically to increased serotonergic activity and can be induced with tryptophan plus a monoamine

oxidase inhibitor, 5-HTP, or 5-HT receptor agonists (Klawans et al., 1973; Luscombe et al., 1982). This behavior can be suppressed by non-specific 5-HT receptor antagonists (Goetz and Klawans, 1974). In the past decade, numerous 5-HT receptor subtypes have been identified anatomically and neurochemically (Gozlan et al., 1983; Hartig et al., 1996; Heuring and Peroutka, 1987; Hoyer et al., 1988, 1994; Leonhardt et al., 1989; Leysen et al., 1982; Peroutka, 1986). Recently, relatively specific receptor agonists and antagonists have been developed that allow more refined pharmacologic and neurochemical analysis of behaviors that relate to 5-HT. To date, these agents have not been studied in the myoclonic jumping behavior model. Our study demonstrates that myoclonic jumping behavior is not suppressed by all agents that act as 5-HT receptor antagonists. Rather, only mesulergine hydrochloride, methiothepin mesylate, and GR-127935 suppressed myoclonic jumping behavior. Each drug reduced myoclonic jumping behavior in a dose-dependent fashion. At the doses studied, only methiothepin mesylate completely abolished myoclonic jumping behavior. The apparent biphasic effects of mesulergine and GR127935 on myoclonic jumping behavior antagonism may indicate that more than a single mechanism or receptor subtype may be associated with these effects.

Although we studied a series of agents that affected a large array of receptor subtypes, the drugs that reduced myoclonic jumping behavior have effects that are largely isolated to the 5-HT_1 and 5-HT_2 receptors. Mesulergine hydrochloride blocks primarily the 5-HT_{2C} receptors with affinity for the other two 5-HT_2 receptor subtypes; methiothepin mesylate affects 5-HT_1 and 5-HT_2 receptors, and GR-127935 is a relatively specific antagonist of the 5-HT_{1D} receptor without marked activity at 5-HT_2 receptors. SR46349 is a 5-HT_2 receptor antagonist and was also observed to attenuate myoclonic jumping behavior although the effects did not reach statistical significance or produce the a priori criterion of a 50% reduction in myoclonic jumping behavior. Regardless, its attenuation of myoclonic jumping behavior is consistent with the hypothesis that myoclonic jumping behavior is a 5-HT_1 and 5-HT_2 receptor mediated phenomenon, and further studies of these receptor subtypes are planned.

Other investigators have evaluated myoclonic jumping behavior using relatively selective 5-HT receptor agonists. Eison et al. (1993) induced myoclonic jumping behavior using 5-MeODMT (a mixed 5-HT_{1A}/5-HT_2 receptor agonist) at high doses, but could not elicit myoclonic jumping behavior with low doses of this drug, with 8-OH-DPAT (a selective 5-HT_{1A} receptor agonist) or DOI (a selective 5-HT_2 receptor agonist) by themselves. These unblinded, non-placebo-controlled findings suggest that myoclonic jumping behavior may relate to receptor site interactions between the 5-HT_1 and 5-HT_2 systems or that the studied drugs may not be receptor specific at high doses. In the only other evaluation of selective serotonergic antagonists in this guinea pig model, Hutson et al. (1995) used a different protocol from ours and compared GR 127935 to GR 127935 with 5-HTP without a control group receiving 5-HTP alone. These authors administered GR 127935 in the low and moderate dosage range of our dose-response study (0.1–3.0 mg/kg) 1 h before low dose 5-HTP (10 mg/kg without carbidopa pre-treatment) compared to 75 mg/kg with carbidopa in our study. They counted head jerks for 20 min beginning 10 min after 5-HTP injection in an undetermined number of animals. They found no significant difference between the number of head jerks observed with GR 127935 alone compared to when it was given with 5-HTP. The differences in dosages, treatment times, behavioral measures and control groups make direct comparisons of our data sets difficult. The very clear dose-response effects seen in our study and the high density of 5-HT_{1D} receptors in the guinea pig brain stem suggest that this system should be evaluated further.

Our study focused on the acute administration of serotonergic drugs with agents of relative receptor subtype specificity. Pharmacological investigations with newer receptor subtype specific agents affecting isolated receptor classes will further delineate the neurochemical basis of this animal model. Data on chronic effects of 5-HT receptor antagonists relative to myoclonic jumping behavior are especially important to extrapolations to clinical medicine, since non-epileptic myoclonus in humans is a persistent disability. To date, no selective antagonists for the 5-HT_1 and 5-HT_2 receptors are available for human study, but our data suggest that when antagonists of these receptor subtypes emerge, a reasonable application will include non-epileptic myoclonic disorders.

Acknowledgements

This work was supported by a grant from the Myoclonus Research Foundation, the United Parkinson Foundation, and NS 33174. We appreciated the advice of Professor Michel Hamon.

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