
BRIEF REPORT

Nicotine Blocks Kainic Acid-Induced Wet Dog Shakes in Rats

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Systemic or central administration of kainic acid (KA) in rats results in the expression of wet dog shakes (WDS) followed by motoric seizures and convulsions, which are associated with limbic neurotoxicity. Although a number of neurotransmitter systems are thought to be involved with this KA-induced syndrome, little is known about the possible influence of cholinergic nicotinic receptor modulation. In the study presented here, we pretreated rats with saline or 0.5 mg/kg nicotine base followed 15 minutes later by 12.0 mg/kg KA and then observed the

incidence of WDS between 45 and 120 minutes post-KA injection. Rats pretreated with nicotine exhibited significantly less WDS than those pretreated with saline ($p < .001$). Whereas the mechanism for this nicotine effect is currently not known, future experiments will look at dose-response relationships, the role of nicotine receptors, and possible neuroprotective potential of nicotine in this KA-induced syndrome.

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KEY WORDS: Nicotine; Cholinergic; Kainic acid; Wet dog shakes; Seizures

In adult rats, systemic or intraventricular administration of the glutamate analogue, kainic acid (KA), results in the expression of a syndrome characterized by behavioral automatisms such as wet dog shakes (WDS), motoric seizures, excessive salivation, whole body tremor, aggression, hyperactivity, and brain neurotoxicity (Lenicque et al. 1979). Although many brain areas are affected by KA administration, the hippocampus is most affected (Ben-Ari 1985). The neurodegeneration of cells in the CA3/CA4 regions results in epileptiform activity displayed by CA1 pyramidal cells, which is characterized by an enhanced NMDA-mediated excitatory phase with an apparent loss of GABA-mediated postsynaptic inhibition (Turner and Wheal 1991; Wil-

liams et al. 1993). Because of both the behavioral and neurologic similarities, this KA-induced syndrome has been proposed as an animal model for human temporal lobe epilepsy (Ben-Ari 1985; Williams et al. 1993).

KA-induced WDS are similar to those observed after morphine withdrawal (Fuller and Olney 1979) and are influenced by drugs that affect a number of neurotransmitter and neuropeptide systems including GABA (Lenicque et al. 1979), excitatory amino acids (Dawson and Wallace 1992), serotonin, norepinephrine, dopamine, endogenous opioids (Velíšek et al. 1994; Worms et al. 1981; Fuller and Olney 1979), and substance P (Velázquez et al. 1993).

WDS produced by other drugs have been proposed as an animal model of Tourette's syndrome (Handley and Dursun 1992), a hyperkinetic motor disorder characterized by repeated automatisms such as motor and vocal tics, and we (Sanberg et al. 1988; Silver et al. 1994), as well as others (Reveley et al. 1994), have reported that nicotine may be therapeutically active in reducing tic frequency and severity in these patients. Nicotine is thought to act primarily at acetylcholine nicotinic receptors, where it activates the presynaptic release of acetylcholine, monoamines (Balfour 1982), and

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GABA (Wonnacott et al. 1989). Nicotine has also been found to alter the brain levels of several hormones and neuropeptides (Andersson et al. 1988), including nerve growth factor receptor expression (Terry and Clark 1994). However, little is known about the role of cholinergic systems underlying KA-induced WDS and, to our knowledge, no studies have investigated the effects of nicotinic agonists or antagonists on KA-induced WDS. Therefore, the present experiment was designed to investigate the ability of nicotine to influence the WDS produced by systemic administration of KA.

METHODS

Sixteen experimentally naive, 8 week old, male Sprague-Dawley derived albino rats (~250 g), each received subcutaneous injections of first saline or 0.5 mg/kg nicotine (free base dissolved in saline) followed 15 minutes later by 12.0 mg/kg kainic acid (dissolved in saline and buffered to a pH of 7.2). Based on separate preliminary experiments investigating temporal parameters, rats were observed for rapid axial head and body rotations or "wet dog shakes" (WDS) between 45 and 125 minutes post-KA injection in their home cages. An experimenter, who was blind to the treatment conditions, counted the number of WDS over 5-minute periods at 15-minute intervals. The data were analyzed statistically with the use of an ANOVA with repeated measures followed by post hoc tests (Scheffé) to detect group differences at each time point.

RESULTS

As shown in Figure 1, the incidence of KA-induced WDS was less prevalent in those rats pretreated with nicotine than in those pretreated with saline. This was confirmed by the ANOVA with repeated measures, which indicated a significant effect of "group" ($F = 17.6$; $df = 1,14$; $p < .001$) and "time" ($F = 5.1$; $df = 5,70$; $p < .001$) with a significant "group" by "time" interaction ($F = 4.0$; $df = 5,70$; $p < .005$). Further post hoc analyses revealed that significant group differences occurred at between 80 and 110 minutes post-KA injection ($p < .01$).

Although not explicitly quantified by experimenters, nicotine pretreated rats displayed marked hypoactivity characterized by a flaccid appearance and a tendency to lie outstretched on the cage floor. This hypoactive response subsided rapidly 15 to 20 minutes postnicotine injection at which time the rats' behavior appeared normal.

DISCUSSION

The present findings are in agreement with others who have reported that systemic administration of KA in rats

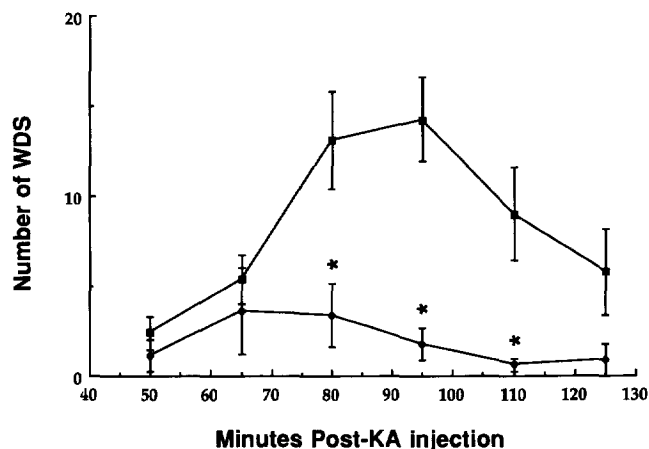


Figure 1. The effects of 0.5 mg/kg nicotine pretreatment on mean WDS produced by 12.0 mg/kg kainic acid for data collected over 5-minute periods at 15-minute intervals. Range bars indicate SEM ($n = 8$ /group) and asterisks indicate significant difference at $p < 0.01$. Upper line with squares represents saline and lower line with diamonds represents nicotine.

at similar doses used in the present experiment produce WDS that peak in appearance at 90 minutes and subside at around 120 minutes postinjection (Worms et al. 1981). Furthermore, we report for the first time that a high dose of nicotine profoundly attenuates the expression of WDS induced by KA.

In agreement with previous behavioral studies using similar doses of nicotine (Clarke and Kumar 1983), nicotine pretreated rats displayed marked hypoactivity which subsided rapidly 15 to 20 minutes postnicotine injection. It is unlikely that this depressant effect of nicotine masked the behavioral effects of KA, as the reduction in KA-induced WDS occurred between 95 and 125 minutes postnicotine injection, at a time when the behavioral effects of nicotine have largely dissipated or may even be slightly stimulatory (Clarke and Kumar 1983). Whether this ability of nicotine to block the WDS produced by KA is pharmacokinetic or pharmacodynamic remains to be determined; however, WDS are observed after withdrawal from chronic nicotine exposure (Malin et al. 1992) suggesting that central nicotinic mechanisms may be involved with the expression of WDS.

Because GABA agonists strongly inhibit both the behavioral and neurotoxic consequences of KA administration (Lenicque et al. 1979; Worms et al. 1981), it is possible that nicotine blocked KA-induced WDS through a GABA-mediated process. In fact, nicotine has been reported to stimulate the spontaneous release of GABA from hippocampal synaptosomes (Wonnacott et al. 1989). On the other hand, it has been reported that the nicotinic acetylcholine receptor shares structural homologies between both GABA_A (Schofield et al.

1987) and glycine receptors (Grenningloh et al. 1987), which may permit nicotine to interact with ligand-gated ion channels other than the nicotinic receptor. In this regard, nicotine has been found to both partially inhibit whole-cell N-methyl-D-aspartate (NMDA) induced responses and displace MK-801, a noncompetitive NMDA receptor antagonist, in rat cortical neurons (Aizenman et al. 1991). Therefore, because NMDA receptor activation is thought to contribute significantly to both the behavioral and neurotoxic effects of systemically administered KA (Clifford et al. 1990), it is possible that nicotine may have inhibited KA-induced WDS by interacting directly with the NMDA receptor complex.

In light of the present findings and the growing body of evidence now suggesting that nicotine may have neuroprotective properties against the neurotoxic consequences of excitatory amino acid exposure (Akaike et al. 1994; Marin et al. 1994), as well as the neurodegeneration produced by surgical brain transection (Janson and Moller 1993), more extensive experiments are warranted to investigate the dose parameters, the roles of peripheral and central nicotinic receptors, and possible neuroprotective potential of nicotine in this KA-induced behavioral and neurodegenerative syndrome.

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