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THE α7 NICOTINIC RECEPTOR AGONIST 4OH-GTS-21 PROTECTS AXOTOMIZED SEPTOHIPPOCAMPAL CHOLINERGIC NEURONS IN WILD TYPE BUT NOT AMYLOID-OVEREXPRESSING TRANSGENIC MICE

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Abstract—While activation of α7 nicotinic receptors protects neurons from a variety of apoptotic insults *in vitro*, little is known about this neuroprotective action *in vivo*, especially under amyloidogenic conditions that mimic Alzheimer's disease. We therefore investigated the effects of 4OH-GTS-21, a selective partial agonist for these receptors, on septohippocampal cholinergic and GABAergic neuron survival following fimbria fornix (FFX) lesions in three strains of mice: C57BL/6J wild type mice; human presenilin-1 mutant M146L (PS1) transgenic mice; and mice expressing both mutant PS1 and Swedish mutant K670N/M671L amyloid precursor protein (APP). Initial studies to demonstrated that 4OH-GTS-21 is likely brain permeant based on its ability to improve passive avoidance and Morris water task behaviors in nucleus basalis–lesioned rats. In FFX-lesioned mice, twice per day i.p. injections of 1 mg/kg of 4OH-GTS-21 for 2 weeks promoted the survival and prevented the atrophy of septal cholinergic neurons. Septal parvalbumin-staining GABAergic neurons were not protected by this treatment, although they also express α7 nicotinic receptors, suggesting an indirect, nerve growth factor (NGF)–mediated mechanism. No protection of cholinergic neurons was observed in similarly treated PS1 or APP/PS1 transgenic mice. 4OH-GTS-21 treatment actually reduced cholinergic neuronal size in APP/PS1 mice. Hippocampal amyloid deposition was not affected by FFX lesions or treatment with this α7 nicotinic receptor agonist in APP/PS1 mice under these conditions. These results indicate that brain α7 nicotinic receptors are potential targets for protecting at-risk brain neurons in Alzheimer's disease, perhaps via their effects on NGF receptors; however, this protection may be sensitive under some conditions to environmental factors such as inhibitory amyloid-peptides. **© 2007 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: 4OH-GTS-21, FFX-lesions, cholinergic neurons, GABAergic neurons, APP/PS1 and PS1 mice.

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Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; ChAT, choline acetyltransferase; FFX, fimbria fornix lesions; NGF, nerve growth factor; PBS, phosphate-buffered saline; PS1, presenilin-1.

Brain α7 nicotinic receptors are involved in cell viability (Ren et al., 2005) and a variety of memory-related and attentional behaviors (Meyer et al., 1998c; Ren et al., 2005). Activation of these receptors can protect neurons and other cells from a variety of apoptotic insults *in vitro*, including nerve growth factor (NGF) deprivation (Li et al., 1999b), glutamatergic excitotoxicity (Shimohama et al., 1998), ethanol-exposure (Li et al., 1999a), amyloid-toxicity (Marrero et al., 2004) and oxygen/glucose deprivation (Egea et al., 2007). α7 Nicotinic receptor activation can also improve spatial and avoidance memory-behaviors in rodents, avoidance behavior in rabbits, delayed matching performance in primates, and word recall in humans (Arendash et al., 1995; Briggs et al., 1997; Meyer et al., 1998c; Woodruff-Pak, 2003; Marubio and Paylor, 2004). α7 Nicotinic receptors have accordingly become targets for treating conditions associated with neuropathological disorders involving neuronal loss and memory deficits such as Alzheimer's disease (AD). However, much less is known about the protective effects of α7 nicotinic receptors *in vivo*, especially in models of AD.

AD is characterized by the presence of large numbers of amyloid-containing plaques, neurofibrillary tangles and the progressive atrophy and loss of neurons. It is also associated with dysfunctions in a variety of neuronal systems, including ascending septal cholinergic neurons that are important for memory-related behavior (Terry and Buccafusco, 2003). One approach to modeling this condition involves transgenic mice expressing mutant forms of human amyloid precursor protein (APP) that lead to elevated levels of amyloid production and amyloid deposits (Puolivali et al., 2002). The APP Swedish mutant K670N/M671L transgenic mouse expresses high levels of the fibrillogenic Aβ1–42 peptide and, eventually, develops extracellular amyloid deposits (Irizarry et al., 1997). Mutations in the gamma secretase-associated protein presenilin 1 (PS1) are also associated with AD, and while transgenic mice expressing this type of mutation (e.g. PS1-M146L) do not exhibit amyloid deposition, they do have elevated brain levels of the fibrillogenic amyloid peptide Aβ1–42 (Duff et al., 1996). The combination of these two transgenes in the APP/PS1 mouse results in a more rapid production amyloid deposition than with APP mutations alone (Kurt et al., 2003), which has led to widespread use of these transgenic animals for studying the amyloidogenic component of AD.

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Another approach to modeling AD involves lesioning selective neuronal pathways selectively affected by the disease, such as septohippocampal cholinergic neurons (Terry and Buccafusco, 2003). These models have proven useful for evaluating potential neuroprotective agents, in part because amyloid-producing transgenic mouse models do not typically demonstrate the neuronal loss seen in AD. This approach has shown that NGF can protect axotomized septal cholinergic neurons from the atrophy and death otherwise induced by fimbria fornix (FFX) lesions (Hefti et al., 1989). This finding, along with other observations demonstrating a role for retrograde NGF-transport from hippocampus to septum in the maintenance of basal forebrain cholinergic neurons (Capsoni and Cattaneo, 2006; Salehi et al., 2006) has led to several clinical trials using NGF for AD.

We hypothesized that activation of α7 nicotinic receptors on septal cholinergic neurons may exert a similar protective, NGF-like, action against the effects of FFX-lesions. Septal cholinergic and GABAergic neurons express functional α7 nicotinic receptors, providing a target for α7 nicotinic agonists (Azam et al., 2003; Thinschmidt et al., 2005a). In addition, nicotinic receptor activation was found to increase the levels of the NGF receptor trkA, apparently through α7 nicotinic receptors (Jonnala et al., 2002). To test this hypothesis, we used a selective α7 nicotinic receptor partial agonist, 4OH-GTS-21 (Meyer et al., 1998b; Uteshev et al., 2003). 4OH-GTS-21 is a more potent and efficacious agonist for α7 nicotinic receptors than is its clinically tested analog GTS-21 (Meyer et al., 1998b). However, since its ability to cross the blood–brain barrier has not been demonstrated, we first investigated whether it improved memory-related behaviors in nucleus basalis lesioned animals, as seen with GTS-21 (Meyer et al., 1997).

A potential concern about the use of α7 nicotinic receptor agonists in AD involves the highly potent inhibition of these receptors by Aβ1–42 (Wang et al., 2000; Liu et al., 2001). It is unclear whether α7 nicotinic receptor functions are attenuated in the AD brain or those of amyloid-overexpressing mice, and if so, whether agonist-treatment can overcome this inhibition. Two recent ex vivo electrophysiological studies reported different effects in the hippocampus of amyloid-depositing mice, one showing little or no attenuation of receptor-function (Spencer et al., 2006) and the other receptor-blockade that was proportional to amyloid-load (Sola et al., 2006). We therefore investigated the protective effects of 4OH-GTS-21 in FFX-lesioned PS1 and APP/PS1 mice to evaluate this potential interaction in a longer-term model of receptor-function *in vivo*.

Chronic exposure to nicotine has been reported to reduce amyloid deposition in APP/PS1 mice (Nordberg et al., 2002), and recently it was found that this effect could be blocked with a selective α7 nicotinic receptor antagonist (Zhang et al., 2006). These results may help elucidate how exposure to tobacco is associated with reductions in amyloid plaque density in the entorhinal cortices of AD patients (Court et al., 2005). While these observations indicate that α7 nicotinic receptors may be necessary for the amyloid-reducing action of nicotine, they do not demonstrate that activation of these receptors is sufficient to elicit the effect. We therefore also investigated whether chronic administration of 4OH-GTS-21 reduced amyloid deposition in APP/PS1 mice with preexisting amyloid-load.

EXPERIMENTAL PROCEDURES

Passive avoidance and Morris water task behaviors

Passive avoidance and Morris water task behaviors were measured in nucleus basalis lesioned rats after i.p. injections of 4OH-GTS-21 or saline controls. For lesions, male 5-month-old Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA, USA) were anesthetized with 50 mg/kg sodium pentobarbital (i.p.) and then infused bilaterally with 1 μl of 5 μg/μl ibotenic acid in phosphate-buffered saline (PBS), pH 7.4, into the nucleus basalis as described previously (Meyer et al., 1997). Infusion coordinates were anterior 7.0 mm, lateral 2.6 mm and vertical 6.5 mm according to Paxinos et al., (1985). Unlesioned control rats received sham surgeries only. Following surgery, animals were returned to their home cages and fed semi-solid mash made from Purina rat chow for several days. One month later, animals were trained in a two-chamber passive avoidance paradigm. Animals received i.p. injections of either 1 ml/kg 0.9% saline diluent or specified doses of 4OH-GTS-21 (salt weight). Fifteen minutes after injections, animals were placed in the lit compartment, and allowed to enter the adjoining dark chamber. Each animal entered the dark chamber within the 5-min cutoff training interval. Those animals that entered the second chamber received a mild foot shock (0.8 mA) for 1 s. Rats were tested for latency 24 h later for up to 5 min; this test also began 15 min after the same drug- or saline-injection. All experiments conformed to U.S. National Institutes of Health and local institutional animal care and use committee guidelines for the ethical use of animals. The number of animals used and their potential suffering were minimized throughout this study.

Morris water task performance, a measure of spatial memory–related behavior, was investigated as described previously (Meyer et al., 1997). Animals received 3 days of 12 training sessions/day beginning in the morning of each day. They were injected with specified doses of 4OH-GTS-21 15 min before the first training session each day. Drug doses were randomly selected relative to those used for passive avoidance behavior. During training, animals were hand-guided to the platform if they did not find it by 60 s; these training intervals were given a 60 s value. Escape latencies were measured for each session and comparisons among groups were determined for each day by one-way ANOVA. Swimming distance was measured for the entire 36 trials for each animal and compared using one-way ANOVA. Histological assessments of the ibotenic acid placements in the nucleus basalis were made after behavioral measurements using cholinesterase staining in formalin-fixed tissues (Meyer et al., 1998a). Lesion-placement and qualitative assessment of loss of cholinergic innervation of the hippocampus were determined with cholinesterase-staining of the septum and hippocampus, respectively as described previously (Meyer et al., 1997).

FFX lesions

Wild type (C57/B16/J) (Jax Laboratories, Bar Harbor, ME, USA) and APP/PS1 (Bl6/D2×Swiss Webster; a gift from Dr. Karen Duff, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA) or PS1 (Swiss Webster×B6D2F1 crosses; Taconic Farms, Germantown, NY, USA) mice were anesthetized with sodium 2–6% isoflurane/oxygen gas. Depth of anesthesia was determined by toe pinch and corneal reflex. Body temperature was maintained at 37 °C with an isothermal pad. The skull was exposed, and the bone from the region overlaying the septal area

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