Janus Kinase 2, an Early Target of α7 Nicotinic Acetylcholine Receptor-mediated Neuroprotection against Aβ-(1–42) Amyloid*

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The molecular mechanisms of α7 nicotinic acetylcholine receptor (nAChR)-mediated neuroprotection remain unclear. In this study we provide evidence that nicotine stimulation of α7 nAChR transduces signals to phosphatidylinositol 3-kinase and Akt via Janus kinase 2 (JAK2) in a cascade, which results in neuroprotection. Exposure to β-amyloid results in the activation of the apoptotic enzyme caspase-3 and cleavage of the DNA-repairing enzyme poly(ADP-ribose) polymerase. This cascade is inhibited by nicotine through JAK2 activation, and these effects are blocked by preincubation with the JAK2-specific inhibitor AG-490. We also found that pretreatment of cells with angiotensin II blocks the nicotine-induced activation of JAK2 via the ATr receptor and completely prevents α7 nAChR-mediated neuroprotective effects further suggesting a pivotal role for JAK2. These findings identify novel mechanisms of receptor interactions relevant to neuronal viability and suggest novel therapeutic strategies to optimize neuroprotection.

The cholinergic deficit in Alzheimer’s disease (AD)3 has been clearly established and is the basis for the current symptomatic strategy. There is an early and significant depletion of high affinity nicotinic receptors in the brains of Alzheimer’s patients (1), and a number of studies have shown cognitive improvement in rodent and primates including humans following administration of ligands targeting nicotinic acetylcholine receptor (nAChR) (2). In addition to their known symptomatic effects, neuronal nicotinic ligands have shown neuroprotective activity in vitro (3) and in vivo (4) suggesting an additional potential for disease modification.

The α7 nAChR forms functional homeric ligand-gated ion channels that promote rapidly desensitizing Ca2+ influx, is widely expressed throughout the mammalian brain, and has been implicated in sensory gating, cognition, and neuroprotection (5). In addition, nicotine-induced neuroprotection against β-amyloid-induced toxicity is suppressed by α-bungarotoxin (α-Bgt), and the selective α7 nAChR agonist, abacavir-de-derived 3-(4)-dimethylaminocinnamylidine, exerts cytoprotective effects (6, 7). Furthermore, a recent study (8), has reported that the levels of phosphorylated Akt, an effector of phosphatidylinositol 3-kinase (PI-3-K), are increased by nicotine and that the nicotine-induced cytoprotective effects are suppressed by the PI-3-K inhibitors (LY294002 and wortmannin). These findings suggest that the α7 nAChR transduces signals to PI-3-K in a cascade, which ultimately contributes to a neuroprotective effect against Aβ-(1–42).

In comparison to the findings above, another study (9) has shown that whereas nicotine activates the PI-3-K neuroprotective cascade, Aβ-(1–42) chronically activates the mitogen-activated protein kinase (MAPK) cascade via the hippocampal α7 nAChR. The investigators suggest that this chronic activation of the MAPK pathway by Aβ-(1–42) eventually leads to the down-regulation of MAPK which then sets a positive feedback for Aβ accumulation and decreased phosphorylation of the cAMP-regulatory protein which is a necessary component for hippocampus-dependent memory formation in mammals (9).

The angiotensin-converting enzyme density is also increased in the temporal cortex from patients with AD (10), and the angiotensin-converting enzyme genotype is associated with AD in some populations (11). The angiotensin II (Ang II) AT1 receptor exerts growth inhibitory effects or apoptosis both in cultured cells and in vivo (12) are expressed in PC12 cells, and have been shown to inhibit the Janus kinase/signal transducers and activators of transcription (JAKSTAT) signaling cascade (13).

In this study we show that nicotine-induced neuroprotection against Aβ-(1–42) is mediated through tyrosine phosphorylation of JAK2, subsequent activation of PI-3-K and Akt, and inhibition of both caspase-3 activity and cleavage of the DNA-repairing enzyme poly(ADP-ribose) polymerase (PARP). In contrast, pretreatment of cells with Ang II blocks the nicotine-induced activation of JAK2 via the AT1 receptor and completely prevents α7 nAChR-mediated neuroprotective effects.

**EXPERIMENTAL PROCEDURES**

The abbreviations used are: AD, Alzheimer's disease; JAK2, Janus kinase 2; MAPK, mitogen-activated protein kinase; PI-3-K, phosphatidylinositol 3-kinase; PARP, poly(ADP-ribose) polymerase; nAChR, nicotinic acetylcholine receptor; α-Bgt, α-bungarotoxin; PC12, rat pheochromocytoma cells; Ang II, angiotensin II; JAKSTATJanus kinase/signal transducers and activators of transcription; 7AMC, 7-amino-4-methylcoumarin.

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obtained in three experiments. Whereas many tyrosine kinase inhibitors are often promiscuous in the enzyme they target, AG-490 is unique in that it does not inhibit other tyrosine kinases such as Lck, Lyn, Btk, Syk, Src, JAK1, or Tyk2 (15). At the end of stimulation, cells were washed twice with ice-cold PBSV (phosphate-buffered saline with 1 mmol/liter Na4VO4). Each dish was then treated for 60 min with ice-cold lysis buffer (20 mmol/liter Tris-HCl, pH 7.4, 2.5 mmol/liter EDTA, 1% Triton X-100, 10% glycerol, 10 mmol/liter Na3P2O7, 50 mmol/liter NaF, 1 mmol/liter Na4VO4, and 1 mmol/liter phenylmethanesulfonyl fluoride), and the supernatant fraction was obtained as cell lysate by centrifugation at 58,000 × g for 25 min at 4 °C. Samples were resolved by 10% SDS-PAGE, transferred to a nitrocellulose membrane, and blocked by a 60-min incubation at 22 °C in TTBS (Tris-buffered saline with 0.05% Tween 20, pH 7.4) plus 5% skimmed milk powder. The nitrocellulose membrane was incubated overnight at 4 °C with affinity-purified anti-phospho-specific JAK2 and Akt antibodies. The nitrocellulose membranes were washed twice for 10 min with TTBS and incubated with goat anti-rabbit IgG horseradish peroxidase conjugate. After extensive washing, the bound antibody was visualized on a Kodak Biomax film using a Pierce Supersignal substrate chemiluminescence detection kit.

**Immunoprecipitation Studies of PI-3-K**—The cell lysate, prepared as described above, was incubated with 10 μg/ml anti-PI-3-K monoclonal antibodies at 4 °C for 2 h and precipitated by addition of 50 μl of protein A/G-agarose at 4 °C overnight. The immunoprecipitates were recovered by centrifugation and washed three times with ice-cold wash buffer (Tris-buffered saline, 0.1% Triton X-100, 1 mmol/liter phenylmethylsulfonyl fluoride, and 1 mmol/liter Na4VO4). Immunoprecipitated proteins were dissolved in 100 μl of Laemmli sample buffer, and 80 μl of each sample were resolved by SDS-PAGE. Samples were transferred to a nitrocellulose membrane and blocked by 60-min incubation at room temperature (22 °C) in TTBS plus 5% skimmed milk powder. The nitrocellulose membrane was then incubated overnight at 4 °C with 10 μg/ml affinity-purified anti-phospho-Akt antibodies, and the bound antibodies were visualized using a Pierce Supersignal chemiluminescence detection kit.

**Assessment of PC12 Cell Apoptosis**—Apoptosis was determined by as-

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**Fig. 1.** Effects of the JAK2 inhibitor AG-490 on nicotine-induced tyrosine phosphorylation of JAK2 and PI-3-K plus serine phosphorylation of Akt. PC12 cells preincubated in the presence or absence of the JAK2 inhibitor AG-490 are stimulated with nicotine for the time indicated. Cells are immunoblotted with phospho-specific and non-phospho-specific anti-JAK2 and anti-Akt antibodies or with anti-PI-3-K antibody. The PI-3-K immunoprecipitated proteins are then immunoblotted with anti-phosphotyrosine and anti-PI-3-K antibodies. Results shown are representative of three experiments.

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**Fig. 2.** A, JAK2 phosphorylation is blocked by α7-bungarotoxin. PC12 cells were stimulated with nicotine for the time indicated in the presence or absence of α7-bungarotoxin, and cells were immunoblotted with phospho-specific and non-phospho-specific anti-JAK2. Similar results were obtained in three experiments. B, effects of nicotine on the JAK2 complex formation with the α7 nAChR. Left panel, PC12 cells were stimulated with nicotine for the time indicated. JAK2 was immunoprecipitated (IP) from lysates with an anti-JAK2 antibody. Immunoprecipitates were then immunoblotted with an anti-α7 antibody. Right panel, PC12 cells were stimulated with nicotine for the time indicated. α7 nAChR was immunoprecipitated from lysates with an anti-α7 nAChR antibody. Immunoprecipitates were then immunoblotted with an anti-JAK2 antibody. Similar results were obtained in three experiments. C, co-immunoprecipitation of α7 nAChR with Aβ-(1–42) amyloid. Equal amounts of PC12 cells membrane proteins prepared from PC12 cells treated with Aβ-(1–42) peptide were immunoprecipitated with anti-α7 nAChR antibody and subjected to Western analysis with anti-α7 nAChR. 1st lane, cells treated with Aβ-(1–42) peptide alone; 2nd lane, cells treated with Aβ-(1–42) peptide in the presence of AG-490. PC12 cells treated with Aβ-(1–42) peptide in the presence of nicotine (Nic.) with or without AG-490 are shown in the 3rd and 4th lanes, respectively.
TBST (25 mM Tris-HCl, pH 7.5, 0.5M NaCl, 0.05% Tween 20). Membranes were blocked for 1 hour at 5°C with 5% nonfat dry milk in PBS. Air-dried membranes were incubated with primary PARP antibody specific for the 85-kDa fragment for 2–3 h at 25°C, rinsed with TBST, and incubated with secondary antibody for 1 h at 25°C. Immunodetection was performed with appropriate antibody using an ECL system (Amersham Biosciences). Fluorescence units were normalized relative to total protein concentration of the cell extract. We performed the assays in triplicate and repeated the experiments three times. In addition we measured the decrease in PC12 cell number using a Coulter counter (model ZM, Coulter, Hialeah, FL).

**RESULTS**

Effects of the JAK2 Inhibitor AG-490 on the Nicotine-induced Tyrosine Phosphorylation of JAK2 and PI-3-K plus Serine Phosphorylation of Akt. PC12 cells were co-incubated in the presence or absence of 0.1 μM Aβ(1–42) and nicotine for the time indicated. Cells were immunoblotted with phospho-specific and non-phospho-specific anti-JAK2 antibodies or with anti-Akt antibodies. PI-3-K-immunoprecipitated proteins were then immunoblotted with anti-phosphotyrosine and anti-PI-3-K antibodies. Results shown are representative of three experiments.

**Fig. 3.** Effects of AG-490 on the Aβ(1–42) amyloid-induced phosphorylation of JAK2. PC12 cells preincubated in the presence or absence of the JAK2 inhibitor AG-490 are stimulated with Aβ(1–42) peptide at 0.1 μM or 1 μM for various times. Cell lysates are immunoblotted with phospho-specific and non-phospho-specific anti-JAK2 antibodies. Results shown are representative of three experiments.

**Fig. 4.** Effects of Aβ(1–42) on nicotine-induced tyrosine phosphorylation of JAK2 and PI-3-K plus serine phosphorylation of Akt. PC12 cells were co-incubated in the presence or absence of 0.1 μM Aβ(1–42) were stimulated with nicotine for the time indicated. Cells were immunoblotted with phospho-specific and non-phospho-specific anti-JAK2 and anti-Akt antibodies or with anti-PI-3-K antibody. The PI-3-K-immunoprecipitated proteins were then immunoblotted with anti-phosphotyrosine and anti-PI-3-K antibodies. Results shown are representative of three experiments.

**Fig. 5.** Effects of the JAK2 inhibitor AG-490 and nicotine on the Aβ(1–42) amyloid-induced activation of caspase-3. PC12 cells were incubated for the duration shown with Aβ(1–42) peptide in the presence or absence of nicotine or nicotine co-incubated with AG-490. Caspase-3 activities are shown as the mean ± S.E. of three independent cultures. Aβ(1–42) treatment resulted in significant increase in caspase-3 activity at the time indicated (*, p < 0.01), and this increase was significantly inhibited by co-incubation with nicotine (**, p < 0.01). Nicotine had no effect in the presence of AG-490.

**Fig. 6.** Effects of AG-490 on nicotine-induced protection against Aβ and Ang II-induced apoptosis. PARP expression was measured from lysates of cells treated for 8 h by Aβ(1–42) peptide or Ang II in the presence or absence of nicotine (Nic) and/or AG-490.
Effects of Nicotine on the JAK2 Complex Formation with the α7 nAChR—To test the hypothesis that JAK2 interacts directly with α7 nAChR we conducted co-immunoprecipitation studies using a rabbit polyclonal anti-JAK2 antibody. We stimulated cultured PC12 cells with nicotine (10 μM) for various times, lysed the cells, and immunoprecipitated JAK2 with anti-JAK2 antibody. Immunoprecipitated proteins were separated by gel electrophoresis, transferred to nitrocellulose, and immunoblotted with anti-α7 nAChR antibodies. As shown in Fig. 2B, nicotine induced a rapid association of JAK2 with the α7 nAChR within 5 min. This time course of α7 nAChR association with JAK2 was similar to that of the nicotine-induced activation of JAK2 (Fig. 1). Similar results were also obtained when the experiments were repeated using α7 nAChR receptor antibody to immunoprecipitate the receptor and to probe the Western blot with the anti-JAK2 antibody (Fig. 2B).

Co-immunoprecipitation of α7 nAChR with αβ(1–42) Amyloid and JAK2 Phosphorylation—Recent studies (17, 18) have shown that αβ(1–42) binds with high affinity to α7 nAChR, and this interaction can be inhibited by α7 nAChR antagonist. In these sets of experiments we confirmed the molecular association between αβ(1–42) and α7 nAChR in cells treated with αβ(1–42) (10 μM for 5 min) and immunoprecipitated with the anti-αβ(1–42) antibodies. Western analyses identified a 57-kDa protein reactive to anti-α7 nAChR which co-immunoprecipitated with αβ(1–42) (Fig. 2C). This effect was not prevented by AG-490 pretreatment of cells (Fig. 2C), and when the cells were co-incubated with 10 μM nicotine the complex formation between αβ(1–42) and α7 nAChR was blocked even in the presence of AG-490 (Fig. 2C). These results suggest that the interaction between αβ(1–42) and α7 nAChR can be inhibited by nicotine independently of JAK2. Furthermore, treatment of PC12 cells with αβ(1–42) (0.1–1 μM) did not induce the tyrosine phosphorylation of JAK2 (Fig. 3) even at higher concentrations (10 and 100 μM; data not shown). Moreover, co-incubation of the cells with 0.1 μM αβ(1–42) had no effect on the nicotine-stimulated JAK2 tyrosine phosphorylation, the tyrosine phosphorylation of PI-3-K, and the serine phosphorylation of Akt (Fig. 4).

Effects of Nicotine on the αβ(1–42)-induced Apoptosis and the Role of JAK2—Caspase-3 is expressed in PC12 cells and is known to be involved in apoptosis. We examined caspase-3 activity following αβ(1–42)-induced apoptosis. We used the fluorescent peptide substrate Ac-DEVD-7AMC to measure caspase-3-like activity in cell lysates. As shown in Fig. 5, the caspase-3-like activity that resulted in the cleavage of the peptide substrate Ac-DEVD-7AMC is evident after 4 h of αβ(1–42) treatment and increased over time until it reached a peak after 8 h of treatment. The αβ(1–42)-induced activation of caspase-3 was blocked by nicotine (p < 0.01), and this inhibition was prevented by AG-490 (Fig. 5).

We explored further the activation of caspase-3 following αβ(1–42) treatment by measuring the cleavage of the DNA-repairing enzyme PARP using Western blot assay. PARP is an endogenous substrate for caspase-3, which is cleaved to a typical 85-kDa fragment during various forms of apoptosis. As shown in Fig. 6, PARP (116-kDa) was cleaved to its 85-kDa fragment following αβ(1–42) treatment. Again, just like the activation of caspase-3, the αβ(1–42)-induced cleavage of PARP was blocked by nicotine, and this inhibition was prevented by AG-490 and Ang II (Fig. 6). This PARP cleavage further indicates that caspase-3 or caspase-3-like proteases are activated in αβ(1–42)-induced cells death.

We tested the involvement of JAK2 in nicotine-induced neuroprotection in the presence or absence of αβ(1–42). We measured the decrease in PC12 cell number using a Coulter counter following αβ(1–42) and Ang II treatments in the presence or absence of nicotine and AG-490. As shown in Fig. 7, cell death induced by αβ(1–42) treatment was significantly reduced in the presence of nicotine (p < 0.01). Nicotine had no effect on αβ(1–42)-induced cell death when co-incubated with AG-490.
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AG-490 on the phosphorylation of both proteins. The initial event is followed by tyrosine phosphorylation of PI-3-K activation of PI-3-K and Akt. We also provide evidence that phosphorylated enzyme JAK2 that results in subsequent activation of JAK2 phosphorylation and inhibition of nicotine-induced neuroprotection as shown by the nicotine-insensitive PARP cleavage and cell viability (Fig. 6 and Fig. 7).

DISCUSSION

In this study we provide evidence for the nicotine-induced complex formation between the α7 nAChR and the tyrosine-phosphorylated enzyme JAK2 that results in subsequent activation of PI-3-K and Akt. We also provide evidence that nicotine interaction with the α7 nAChR is “dominant” over Aβ-(1–42) interaction with the receptor and that the Aβ-(1–42)-induced apoptosis is prevented through the nicotine-induced activation of JAK2. Finally, we also found that the nicotine neuroprotective effects can be neutralized through activation of the angiotensin II AT2 receptor as evidenced by the role for JAK2 phosphorylation and inhibition of nicotine-induced neuroprotection.

Nicotinic neurotransmission is compromised in the brains of AD patients and selective loss of nAChR predominates in brain regions with β-amyloid deposition (1). A direct interaction of the β-amyloid peptide with the α7 nAChR is suggested by recent findings. β-Amyloid peptide interacts with high affinity to the α7 nAChR and results in functional non-competitive blockade in hippocampal neurons (17, 18). In addition, a recent study (9) has also shown that Aβ-(1–42) chronically activates the MAPK cascade via the hippocampal α7 nAChR and that this chronic activation leads to derangement of hippocampal signal transduction in the AD brain. On the other hand, neuroprotective mechanisms mediated by nicotine in clonal cells have implicated the tyrosine phosphorylation of PI-3-K (8), an enzyme involved in phosphoinositide metabolism and linked to cell survival and apoptosis. Anti-apoptotic signals transduced via JAK2 have also been reported. For example, in hematopoietic cells, the kinase domain of JAK2 mediates the induction of Bcl-2 and inhibits cell death (19), and treatment with the JAK2 inhibitor AG-490 reduces the phosphorylation of PI-3-K (20) and STAT3 resulting in an increase in caspase-3 activity and Bax protein in acute myocardial infarction (21). In addition, activation of neuronal erythropoietin receptors prevents apoptosis by triggering cross-talk between the signaling pathways of JAK2 and the nuclear factor-κB (22).

Our findings indicate that α7 nAChR activation induces JAK2 activation via tyrosine phosphorylation and that this initial event is followed by tyrosine phosphorylation of PI-3-K and Akt serine phosphorylation as indicated by the inhibitory effect of AG-490 on the phosphorylation of both proteins. The JAK2 phosphorylation in the presence of nicotine is completely inhibited by α-Bgt, an antagonist to α7 nAChR. Our findings indicate that nicotine-stimulated α7 nAChR results in the formation of a complex between the α7 nAChR protein and JAK2. Because interaction between α7 nAChR and Aβ-(1–42) has been reported based on ligand binding and functional studies, we tested the possibility that β-amyloid could also induce an α7 nAChR-JAK2 complex. Our results confirm the association of β-amyloid and α7 nAChR but indicate no detectable levels of JAK2. In the presence of nicotine, no Aβ immunoreactivity can be detected in the lysate suggesting that nicotine has “displaced” Aβ from α7 nAChR. This effect is independent of JAK2 phosphorylation as shown by the lack of any reversal of this effect in the presence of AG-490.

It is well established that nicotine inhibits Aβ toxicity, but the mechanism is unclear. Our results demonstrate a central role for JAK2 in the α7 nAChR activation of key cellular enzymes involved in cell survival and in inhibition of pro-apoptotic pathways. Nicotine inhibits β-amyloid cytotoxicity, and this effect is completely prevented by inhibition of the tyrosine phosphorylation of JAK2. These effects can be shown by measuring markers of cytotoxicity like the cleavage of the nuclear protein PARP, the induction of caspase-3, or cell viability.

Several reports have documented the apoptotic effects of Aβ II through AT2 receptors. AT2 receptors are expressed in PC12 and have been shown to inhibit the JAK/STAT signaling cascade (23). In contrast to nicotine-induced neuroprotection against β-amyloid-(1–42), pretreatment of cells with Ang II blocks the nicotine-induced activation of JAK2 via the AT2 receptor and completely prevents α7 nAChR-mediated neuroprotective effects further suggesting a pivotal role for JAK2 phosphorylation. Our findings are consistent with opposite roles on cell viability between α7 nAChR and AT2 receptor, activation of the latter overriding the potential benefit through the former (Fig. 9). These results and the convergence of these pathways on phosphorylated JAK2 suggest that recruitment of α7 receptor-mediated neuroprotection against Aβ-(1–42) may be optimized under conditions where AT2-mediated inhibition is minimized. These findings identify novel molecular mechanisms that are fully consistent with the role attributed to α7 nAChR, AT2, and β-amyloid on the pathophysiology observed in the brains of Alzheimer’s patients.

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