Ethanol-sensitive Sites on the Human Dopamine Transporter*

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Previous studies have shown that ethanol enhanced \([\text{[^{3}H]}\text{dopamine uptake in Xenopus oocytes expressing the dopamine transporter (DAT). This increase in DAT activity was mirrored by an increase in the number of transporters expressed at the cell surface. In the present study, ethanol potentiated the function of DAT expressed in HeLa cells but inhibited the function of the related norepinephrine transporter (NET). Chimeras generated between DAT and NET were examined for ethanol sensitivity and demonstrated that a 76-amino acid region spanning transmembrane domains (TMD) 2 and 3 was essential for ethanol potentiation of DAT function. The second intracellular loop between TMD 2 and 3 of DAT, which differs from that of NET by four amino acids, was explored for possible sites of ethanol action. Site-directed mutagenesis was used to replace each of these residues in DAT with the corresponding action. Site-directed mutagenesis was used to replace amino acids, was explored for possible sites of ethanol action. Site-directed mutagenesis was used to replace each of these residues in DAT with the corresponding residue in NET, and the resulting cRNA were expressed in Xenopus oocytes. We found that mutations G130T or I137F abolished ethanol potentiation of DAT function, whereas the mutations F123Y and L138F had no significant effect. These results identify novel sites in the second intracellular loop that are important for ethanol modulation of DAT activity.

The family of Na\(^{+}\) and Cl\(^{-}\)-dependent transporters, which includes the dopamine (DA) and norepinephrine (NE) transporters (DAT and NET, respectively), functions to clear released neurotransmitters from the synaptic cleft (1). DAT regulates the spatial and temporal aspects of dopaminergic synaptic transmission and is an integral part of the mesostriatal DA system. This system plays a central role in mediating the rewarding and reinforcing effects of various drugs of abuse, including ethanol (2–4). DAT is also the site of action for various psychostimulants such as cocaine and amphetamine (1). The function of monoamine transporters at the cell membrane is regulated by multiple second messenger systems; this regulation involves redistribution of the transporters at the cell surface rather than changes in rate of flux of substrate. For example, activation of protein kinase C (PKC) and drugs of abuse such as amphetamine inhibit DAT function by causing internalization of cell surface transporters in a dynamin- and clathrin-dependent manner (5–7). Experiments carried out in human embryonic kidney (HEK-293) cells demonstrated that acute exposure to cocaine enhances DAT activity in a time-dependent manner by increasing the number of functional transporters at the cell surface (8). Cocaine also increases the number of DAT binding sites in neuro2A (N2A, derived from mouse neuroblastoma) cells by altering the intracellular trafficking of DAT (9).

Ethanol has been shown to affect the function of several members of the Na\(^{+}\) and Cl\(^{-}\)-dependent family of transporters. Experiments in HEK-293 cells stably transfected with glycine transporters (GLYT1 and GLYT2) have shown that relatively high concentrations of ethanol (100–200 mM) inhibit uptake of \([\text{[^{3}H]}\text{glycine by GLYT2 and potentiate \([\text{[^{3}H]}\text{glycine uptake by GLYT1 (10). Also, acute exposure to ethanol has been shown to enhance serotonin transporter activity in rat cortical, hippocampal, and brainstem synaptosomes (11). Acute ethanol (10–100 mM) enhances DAT-mediated \([\text{[^{3}H]}\text{DA uptake and transporter-associated currents in a time- and concentration-dependent manner (12). This potentiation of transporter function was accompanied by an increase in the number of functional cell surface transporters, suggesting that ethanol affects transporter function by altering the steady state trafficking of DAT to the cell surface. In contrast, electrochemical experiments suggest that NET function is inhibited by ethanol (13).

DAT shares a high degree of sequence homology with NET (14), but results outlined above suggest that ethanol may have different effects on DAT and NET function. In the present study, we have used the contrasting effects of ethanol on DAT and NET function to identify critical amino acids in DAT that are important for ethanol action. DAT/NET chimeras were expressed in HeLa cells to identify discrete structural domains on DAT and NET that are important for ethanol regulation of transporter function. Site-directed mutagenesis experiments were then carried out, and mutant transporters were functionally analyzed to pinpoint individual amino acid residues that may be crucial for ethanol enhancement of DAT function.

**EXPERIMENTAL PROCEDURES**

**Transporter Chimeras**—Chimeras between the human NET (15) and rat DAT (1) were constructed using a restriction site-independent method as previously described (16, 17). Sequence analysis (partial) identified the precise location of each chimera junction and confirmed that the junction was in-frame. Previous data indicate that most junctions within conserved regions of DAT and NET are not disruptive of transporter function (18, 19). A graphic representation of each chimera is shown in Fig. 1.

**Substrate Uptake in Transfected Mammalian Cells**—Wild type and chimeric transporter cDNA were expressed in HeLa cells using the...
with 2.5 mM Na pyruvate, 0.5 mM theophylline, 100 units/ml penicillin, MgSO₄, 1.2 KH₂PO₄, 5 Tris, 10 HEPES, pH 7.4. Cells were preincubated at 37 °C in KRTH medium containing (in mM): 120 NaCl, 4.7 KCl, 2.2 CaCl₂, 1.2 MgSO₄, 1.2 KH₂PO₄, 5 Tris, 10 HEPES, pH 7.4. Cells were preincubated for 1 h at 37 °C in 500 µl of KRTH in the absence or presence of dopamine (20, 40, 60, or 100 mM). Uptake was initiated by the addition of [3H]dopamine or [3H]WIN 35,428. Nonspecific binding was determined using 3-PPP (R(1)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrochloride). Binding was terminated by rapid filtration and washing using a vacuum manifold.

**RESULTS**

**Effect of Ethanol on Wild Type DAT and NET Expressed in HeLa Cells**—Wild type DAT and NET were expressed in HeLa cells, and the effect of ethanol on [3H]dopamine and [3H]noradrenaline accumulation into these cells was measured. In DAT-expressing cells, ethanol (20–100 mM) significantly increased [3H]DA uptake in a concentration-dependent manner, with 60 mM ethanol producing an ~50% increase in DA uptake (Fig. 2A). In contrast, in NET-expressing cells, ethanol (40–100 mM) inhibited [3H]NE uptake by as much as 22% (Fig. 2B) but had no effect on NET-mediated [3H]DA uptake (Table I).

**Functional Analyses of the Chimeric Transporters**—Chimeric transporters were prepared by sonication six DAT (wild type or mutant)-expressing oocytes in 0.5 ml of ice-cold FRB. Binding to oocyte homogenates was performed in 0.5 ml of FRB containing 4 nM [3H]WIN 35,428. Nonspecific binding was determined using 3-PPP and [3H]DA uptake by ethanol similar to DAT (Table I). In contrast, chimeras NET/DAT or DAT/NET according to their relative orientations and numbered to indicate the TMD nearest its junction. These chimeras depicted DAT uptake characteristics similar to wild type DAT.
two chimeras was similar to DAT and NET, respectively (Table I). Furthermore, we also tested chimeras DAT/NET9, DAT/NET10, NET/DAT10, and NET/DAT11 with junctions downstream of TMD3 (TMD9, TMD10, and TMD11, respectively) for ethanol effects. These chimeras demonstrated ethanol sensitivities comparable to the NET/DAT3 and DAT/NET3 and further delineated the TMD 1–3 region to 76 amino acid residues spanning positions 78–154.

Site-directed Mutagenesis of DAT—Mutagenesis studies were carried out in human DAT to pinpoint sites of ethanol action within the TMD 1–3 region. Because intracellular loops are more accessible for proteins that modulate trafficking (20), we explored the intracellular loop between TMD 2 and TMD 3 for possible sites of ethanol action. The second intracellular

Table I
Effect of ethanol on [3H]DA uptake in HeLa cells expressing wild type DAT, NET, and chimeric transporters

Maximal effective concentrations of ethanol (40–100 mM) were chosen for each chimera. Uptake was initiated by the addition of 10 nM [3H]DA for 20 minutes.

| Enhancement of DA uptake by ethanol | K_m DA | K_m NE |
|-----------------------------------|--------|--------|
| % of control                      | μM     | μM     |
| WT DAT                            | 178 ± 19a | 3.0 | 5.0 |
| WT NET                            | 103 ± 5  | 0.2 | 0.4 |
| NET/DAT1                          | 147 ± 15a | 3.0 | 3.0 |
| DAT/NET1                          | 99 ± 5   | 0.2 | 0.4 |
| NET/DAT3                          | 101 ± 7  | 0.8 | 1.7 |
| DAT/NET3                          | 143 ± 16a | 1.0 | 2.0 |
| NET/DAT10                         | 112 ± 20 | 0.6 | 0.9 |
| DAT/NET9                          | 172 ± 25a | 2.0 | 2.0 |
| NET/DAT11                         | 116 ± 21 | 0.3 | 0.4 |
| DAT/NET10                         | 158 ± 18a | 2.0 | 2.0 |

*p < .05 as compared to respective controls.
loop differs between DAT and NET by only four amino acids, at positions 123, 130, 137, and 138. Each of these amino acids in DAT was replaced with the corresponding amino acid from NET. The resulting cDNA were transcribed in vitro and expressed in *Xenopus* oocytes.

Oocytes expressing wild type and G130T mutant DAT were exposed to ethanol for 1 or 4 h, and [3H]DA uptake was measured. The time periods were chosen to examine the effects of ethanol on [3H]DA uptake as a function of ethanol exposure time. Basal [3H]DA uptake in this mutant was 1.2 fmol/sec/oocyte, which was comparable with that of wild type DAT uptake (1.0 fmol/sec/oocyte). Wild type DAT-expressing oocytes showed a 50% potentiation of [3H]DA uptake after 4 h of ethanol exposure. In contrast, the potentiating effects of ethanol were observed after 1 h of exposure to ethanol for 4 h (Fig. 3). Amino acids phenylalanine at position 123, isoleucine at position 137, and leucine at position 138 were also mutated to the corresponding amino acids in NET (F123Y, I137F, and L138F, respectively). [3H]DA uptake in these mutants was comparable with that of wild type DAT uptake (data not shown). Maximum potentiation of transporter function was observed after 1 h of ethanol exposure in oocytes expressing the wild type transporter (Fig. 4). After exposure to 100 mM ethanol for 1 h, potentiation of [3H]DA uptake was not observed in the mutant I137F (Fig. 4). The mutant F123Y showed ethanol sensitivity comparable with that of wild type DAT (Fig. 4). Ethanol sensitivity of the mutant L138F was reduced but not significantly, compared with that of wild type DAT (Fig. 4).

Previously, we showed that ethanol potentiation of DAT activity was mirrored by an increase in the density of cell surface transporters (12). Upon exposure to ethanol for 1 and 4 h, [3H]WIN 35,428 binding was significantly increased by 40 and 53%, respectively (12). We investigated cell surface transporter numbers in the mutant G130T DAT in the presence, and absence of ethanol by measuring [3H]WIN 35,428 binding. G130T DAT cell surface density was ~20 fmol/oocyte. Ethanol had no significant effect on the number of cell surface transporters in the mutant G130T (Fig. 5).

To test whether ethanol inhibits DAT function when the second intracellular loop is replaced with that of NET, we substituted the second intracellular loop of DAT with that of NET by sequentially mutating positions Phe-123, Gly-130, Ile-137, and Leu-138 to the corresponding amino acids in NET. This loop replacement mutant is termed IGLF. [3H]DA uptake and [3H] WIN 35,428 binding were measured in this mutant and compared with wild type. [3H]DA uptake was not observed in the mutant IGLF. C, homogenates of oocytes expressing wild type and IGLF transporters assayed for [3H]WIN 35,428 binding. Similar levels of binding were detected in both wild type and mutant-expressing oocytes. Mean values ± S.E. are shown for *n* = 6 oocytes per condition from 3–4 batches of oocytes. *, *p* < 0.05; **, *p* < 0.005 as compared with wild type by Student’s t test.

**DISCUSSION**

Previous studies carried out in the *Xenopus* oocyte expression system have shown that acute ethanol (10–100 mM) enhances [3H]DA uptake and transporter-associated currents in a time- and concentration-dependent manner. Ethanol-induced increases in cell surface DAT were not associated with increased protein synthesis (12) but were associated with increased cell surface binding. These results suggest that ethanol enhancement of transporter function may involve redistribution of DAT at the cell surface. The goal of this study was to determine regions on DAT that are critical for ethanol action. NET, which also belongs to the Na\(^+\) and Cl\(^-\)-dependent family of neurotransmitter transporters, shares a high degree of homology (64%) with DAT (14), but in *vivo* electrochemical studies have shown that ethanol inhibits rather than enhances NET function (13).

We used chimeras between DAT and NET and site-directed mutagenesis studies to define critical ethanol-sensitive sites in the second intracellular loop of the transporter. The kinetic parameters of DA uptake (*K_m* and *V_max*) in most of these chimeras were nearly identical to wild type DAT. These chimeras showed that ethanol enhancement of DAT-mediated [3H]DA uptake required the presence of TMD 1–3. Replacing this region of DAT with the corresponding region from NET resulted in abolition of ethanol effects. Chimeras NET/DAT1 and DAT/NET1 with junctions in TMD1 had ethanol sensitivities comparable with DAT and NET, respectively. In contrast, chimeras NET/DAT3 and DAT/NET3 with junctions at TMD3 have ethanol sensitivities comparable with NET and DAT. Also, chimeras with junctions downstream of TMD3 (NET/DAT10 and -11, DAT/NET9 and -10) resemble NET/DAT3 and
DAT/NET3 in their ethanol sensitivities. Taken together, these results indicate that a 76-amino acid region spanning TMD1–3, including the second intracellular loop, is critical for mediating ethanol enhancement of DAT function.

Because intracellular loops are accessible at all times to modifying enzymes and accessory proteins that modulate trafficking (20), we explored the second intracellular loop between TMD2 and TMD3 for possible sites of ethanol action. This loop in DAT differs from that of NET by four amino acids. Site-directed mutagenesis was carried out to substitute glycine at position 130 for threonine, the corresponding amino acid in NET. [3H]DA uptake in this mutant was comparable with that of the wild type DAT. However, ethanol potentiation of [3H]DA uptake was abolished completely in this mutant. Using [3H]WIN 35,428 binding, we examined cell surface expression of this mutant before and after ethanol exposure. [3H]WIN 35,428 binding to the wild type DAT is Na+-dependent, and low intracellular concentrations of sodium ions in the oocyte prevented [3H]WIN 35,428 from binding to intracellular DAT (21, 22). Ethanol had no effect on the number of cell surface G130T mutant transporters, indicating that this amino acid is critical for ethanol-mediated increases in [3H]DA uptake. This suggests that ethanol affects DAT function by altering cell surface distribution of the transporters.

We also mutated amino acids Phe-123, Ile-137, and Leu-138 to the corresponding amino acids in NET. We found that I137F abolished ethanol potentiation of [3H]DA uptake, whereas the other mutations demonstrated ethanol sensitivities comparable with the wild type DAT. Robust changes in ethanol sensitivities were observed in the G130T and I137F mutants, which are non-conservative amino acid changes. No change in ethanol sensitivity was observed in the F123Y mutant, which is a conservative amino acid change. However, the mutant L138F did not demonstrate significant attenuation of ethanol sensitivity despite being a non-conservative mutation. We generated the mutant transporter IGLF to investigate whether replacing the second intracellular loop of DAT with that of NET would result in ethanol inhibition of [3H]DA uptake. However, this mutant transporter does not demonstrate [3H]DA uptake and expresses a significantly lower number of functional transporters at the cell surface. Oocyte fractionation studies indicate that the transporters are synthesized but not trafficked to the cell surface. This result, though unexpected, supports the hypothesis that the second intracellular loop is important for steady state insertion of DAT to the cell surface.

There is now an emerging literature on mutations that affect ethanol actions on ion channels, and it is of interest to compare our analysis of catecholamine transporters with studies of other proteins. Discrete amino acid residues located either in TMD or in the cytoplasmic regions are required for ethanol action on ion channels (23). For example, mutation of Ser-267 at TMD2 of the glycine receptor α1-subunit to isoleucine results in an alcohol-insensitive receptor (24). A transmembrane phenylalanine residue is important for ethanol inhibition of N-methyl-D-aspartate receptors (25). Alcohol modulation of the G-protein-coupled inwardly rectifying the potassium channel (GIRK) function requires a 48-amino acid region in the intracellular C-terminal region of the protein (26). Similarly, ethanol action on voltage-sensitive potassium channels ( Kv1) requires the presence of a discrete amino acid residue in the putative cytoplasmic region of the protein (27). Ethanol indirectly affects the function of metabotropic glutamate receptors (mGluR1) by enhancing PKC-mediated receptor phosphorylation (28). Mutation of a consensus PKC phosphorylation site, Ser-890, abolishes ethanol regulation of receptor function. None of these sites appears to be important for protein trafficking; in contrast, our results identify novel amino acid residues in the second intracellular loop of DAT that are necessary for ethanol modulation of DAT function by a mechanism that is consistent with altered trafficking of the protein to the cell surface.

A common theme in the functional regulation of the Na+/Cl−-dependent family of transporters is the redistribution of cell surface transporters. Several agonists and antagonists of γ-aminobutyric acid and serotonin transporters have been shown to alter subcellular distribution of these transporters (29, 30). PKC activators such as phorbol 12-myristate 13-acetate down-regulate DAT function by causing internalization of cell surface DAT (5, 6, 31). Protein tyrosine kinase A inhibitors have been shown to inhibit DAT function by internalization of cell surface DAT (32). Drugs of abuse have also been shown to alter cell surface DAT densities in some but not all studies. For example, amphetamine decreases cell surface DAT levels by endocytosing the transporter in a dynamin- and clathrin-dependent manner in HEK-293 cells (7). More recently two independent studies have shown that cocaine causes an increase in cell surface DAT levels (8, 9). These studies, carried out in N2A and HEK-293 cells, demonstrate that cocaine-induced enhancement in cell surface DAT levels is due to increased rates of insertion of DAT at the cell surface. Also, dopamine D2 receptor activation affects DAT function by increasing the number of functional cell surface transporters (33). Our results, which suggest that ethanol-mediated functional regulation of DAT involves redistribution of cell surface transporters and that this redistribution involves discrete regions on the transporter, fit very well with this common theme in transporter regulation.

The absence of consensus sites for PKC or for protein tyrosine kinase A phosphorylation in the second intracellular loop suggests that ethanol regulation of DAT function may not be due to increased phosphorylation of the protein. Furthermore, it has been demonstrated that direct phosphorylation of the transporter is not required for functional regulation by PKC (34). It is likely that accessory proteins aid in the functional regulation of DAT, but these remain largely unknown. Recent studies using yeast two-hybrid techniques have identified candidate proteins that interact with the C-terminal tail of DAT and regulate transporter function. For example, α-synuclein interacts with DAT in neurons, and the resulting DAT-α-synuclein complex has been shown to be essential for clustering of DAT at the cell surface and thereby accelerating cellular DA uptake and DA-induced apoptosis (35). The C-terminal tail of DAT also contains a conserved PDZ domain that interacts with the protein PICK1; this interaction is crucial for proper targeting and functioning of DAT (36). Based on our mutants, we hypothesize that ethanol modulates the interaction between DAT and a putative regulatory protein important for ethanol-induced trafficking of DAT and that this interaction occurs at the second intracellular loop. The ethanol-insensitive mutants described in the present work will aid in testing this hypothesis.

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