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# 5-Iodo-2-Aminoindan, a Nonneurotoxic Analogue of *p*-Iodoamphetamine

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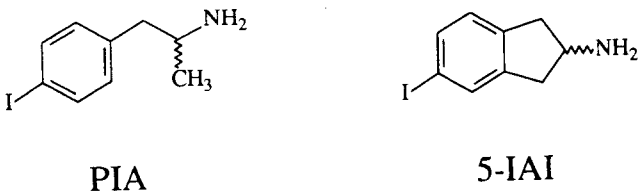
NICHOLS, D. E., M. P. JOHNSON AND R. OBERLENDER. *5-Iodo-2-aminoindan, a nonneurotoxic analogue of p-iodoamphetamine*. PHARMACOL BIOCHEM BEHAV **38**(1) 135–139, 1991.—A rigid analogue, 5-iodo-2-aminoindan (5-IAI), of the serotonin neurotoxic halogenated amphetamine *p*-iodoamphetamine (PIA) was pharmacologically evaluated for production of serotonin neurotoxicity. A comparison was also made between 5-IAI and PIA in the two-lever drug discrimination paradigm in rats trained to discriminate saline from 3,4-methylenedioxymethamphetamine (MDMA) or saline from the α-ethyl homologue of MDMA, MBDB. PIA and 5-IAI were both behaviorally active, and fully substituted in both groups of animals, but were considerably less potent than *p*-chloroamphetamine (PCA). PIA had about twice the potency of PCA as an inhibitor of [$^3$H]-5-HT uptake in rat brain cortical synaptosomes, while 5-IAI was only about 75% as potent as PCA in this assay. A single 40 mg/kg dose of PIA resulted in a 40% reduction of 5-HT and 5-HIAA levels and in the number of 5-HT uptake sites in rat cortex at one week sacrifice. The same dose of 5-IAI with one week sacrifice led to about a 15% decrease in 5-HIAA levels and number of 5-HT uptake sites, but only the latter was statistically significant. In rat hippocampus, PIA gave significant decreases in all serotonin markers examined, while 5-IAI slightly but significantly decreased only 5-HT levels. Neither compound produced any change in catecholamine or catecholamine metabolite levels. The results confirm earlier reports of the selective serotonin neurotoxicity of PIA, which is less severe than that of PCA, and also demonstrate that its rigid analogue 5-IAI does not appear to cause significant serotonin deficits in the rat.

*p*-Iodoamphetamine (PIA) *p*-Chloroamphetamine (PCA) Serotonin Neurotoxicity HPLC-EC Iodoaminoindan

IT is now well established that *p*-chloroamphetamine (PCA) produces a short-term reversible and a long-term irreversible depletion of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) (5, 6, 10). More recent work has suggested that the long-term irreversible depletion of 5-HT is due to a selective degeneration of fine axons originating from the dorsal raphe nucleus (13). In addition to the extensive work with PCA itself, certain studies have reported on both the short-term and long-term effects of structural analogues of PCA. For example, the conformationally rigid analogue 6-chloro-2-aminotetralin retains acute serotonergic actions, but does not cause long-term irreversible depletion of 5-HT similar to PCA (4). These results have been recently confirmed in our laboratory (unpublished results). The loss of serotonin neurotoxicity following rigidification of the side chain of substituted amphetamines was further illustrated when applied to 3,4-methylenedioxy-substituted compounds. Specifically, 3,4-methylenedioxyamphetamine (MDA) causes serotonin neurotoxicity similar to PCA (18), but the rigid analogues, 5,6-methylenedioxy-2-aminoindan (MDAI) and 6,7-methylenedioxy-2-aminotetralin (MDAT) do not appear to possess this action (14).

Another series of structural analogues of PCA results when the chlorine atom is replaced to give other *p*-halogenated amphetamines. Earlier studies have included comparisons of *p*-chloro, *p*-fluoro, *p*-bromo and more recently *p*-iodoamphetamine (3,7). *p*-Iodoamphetamine (PIA) resembled PCA in many respects, including its tissue distribution, half-life, and ability to inhibit [$^{14}$C]-5-HT uptake and block degradation of 5-HT by mitochondrial monoamine oxidase. The long-term depletion of 5-HT characteristic of PCA also occurred with PIA and, as with PCA, these long-term deficits were prevented by pretreatment with the 5-HT uptake inhibitor, fluoxetine (7).

The present report describes pharmacological data for a rigid analogue of PIA, 5-iodo-2-aminoindan (5-IAI; Fig. 1). It was




PIA 5-IAI

FIG. 1. Structures of *p*-iodoamphetamine (PIA) and 5-iodo-2-aminoindan (5-IAI).

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TABLE 1A

SUBSTITUTION IN MDMA-TRAINED ANIMALS

| Drug | Dose (mg/kg; μM/kg) | N* | D† | %SDL‡ | $ED_{50}$§ mg/kg | $ED_{50}$§ μM/kg |
|---|---|---|---|---|---|---|
| PCA (mol.wt. = 207) | | | | | 0.17¶ (0.09–0.32) | 0.84 (0.46–1.55) |
| PIA (mol.wt. = 298) | 0.5; 1.68 | 8 | 0 | 13 | 1.16 (0.78–1.74) | 3.91 (2.61–5.85) |
| | 1.0; 3.36 | 8 | 0 | 38 | | |
| | 1.5; 5.04 | 9 | 1 | 50 | | |
| | 2.0; 6.72 | 9 | 1 | 88 | | |
| 5-IAI (mol.wt. = 296) | 0.125; 0.42 | 9 | 0 | 22 | 0.65 (0.25–1.70) | 2.19 (0.83–5.75) |
| | 0.25; 0.85 | 9 | 1 | 38 | | |
| | 0.5; 1.69 | 9 | 1 | 50 | | |
| | 1.0; 3.38 | 8 | 0 | 50 | | |
| | 2.0; 6.77 | 10 | 2 | 50 | | |
| | 3.0; 10.14 | 11 | 3 | 88 | | |

envisioned that 5-IAI might retain the short-term actions of PIA but lack the long-term neurodegeneration associated with PIA and PCA. In addition, it was anticipated that radiolabelled [$^{125}$I]-PIA [as suggested by Fuller et al. (7)], and [$^{125}$I]-5-IAI might be useful to visualize binding sites in brain utilizing autoradiography techniques.

## METHOD

### *Materials*

PIA·HCl, 5-IAI·HCl, MDMA·HCl and (+)-MBDB·HCl were synthesized in our laboratories using standard procedures (15). All spectral and elemental analyses were consistent with the expected structures. Fluoxetine·HCl was kindly provided by Eli Lilly laboratories (Indianapolis, IN). The HPLC-EC standards were purchased from Sigma Chemical Co. (St. Louis, MO). [$^3$H]-Paroxetine was purchased from New England Nuclear (Boston, MA) at a specific activity of 28.8 Ci/mmol. [$^3$H]-5-HT was purchased from Amersham (Arlington Heights, IL) at a specific activity of 9.3 Ci/mmol.

### *Animals*

Male Sprague-Dawley rats (175 to 200 g) were used in all experiments. Animals were individually caged in a temperature-controlled room with a 12/12 h lighting schedule. Rats used in neurotoxicity tests were given food and water ad lib, while rats used for drug discrimination testing were given free access to water and enough food to maintain them at about 80% of their free-feeding weight. Animal brain dissections were done over ice and the areas removed according to the procedure of Glowinski and Iversen (8). Brain areas from each hemisphere were separated and frozen with liquid nitrogen before storing at −70°C until assay.

### *Drug Discrimination*

The procedures and equipment employed have been described in detail (17). Briefly, rats were trained to discriminate either MDMA·HCl (1.75 mg/kg) or *S*-MBDB·HCl (16) (1.75 mg/kg) from saline using a fixed ratio (FR-50) schedule of food reinforcement. Intraperitoneal injections were given 30 min prior to sessions. Test sessions were separated by at least one drug and one saline maintenance session. Test sessions ended after 5 min or when 50 responses were made on either lever, whichever came first. If 5 min passed without the rat emitting 50 responses, the animal was scored as disrupted and was not used in the calculation of the $ED_{50}$. Animals were not tested if, in the preceding maintenance sessions, the rat gave less than 85% responding on the correct lever prior to the first reinforcement. Following the procedure of Colpaert et al. (2), test data were discarded and the condition later retested if the rat responded incorrectly in either of the following two maintenance sessions. At least eight rats were tested at each dose.

### *HPLC With Electrochemical Detection*

The frontal cortex or hippocampal regions from one hemisphere in each rat were weighed, and homogenized in 0.5 ml of 0.4 N $HClO_4$ containing 0.05% $Na_2EDTA$, and 0.1% $Na_2S_2O_5$ using a motor-driven teflon pestle and Eppendorf 1.5 ml centrifugation tubes. An internal standard of 3-(3,4-dihydroxyphenyl) propionic acid (100 ng/ml, DHPPA) was used. The samples were centrifuged for 4 min at 14,000 × g and the supernatant was assayed for the levels of NE, DA, DOPAC, HVA, 5-HT, and 5-HIAA. The HPLC-EC system consisted of a Brownlee C18 analytical cartridge column (Anspec, Ann Arbor, MI), a refrigerated autosampler (TosoHass, Philadelphia, PA) and a Model 400 EG&G Princeton electrochemical detector (Princeton, NJ). The dual electrode potentials were set at $E_1 = -200$ mV and $E_2 = 850$ mV versus the Ag/AgCl reference electrode. The mobile phase consisted of 0.05 M $NaH_2PO_4$, 0.03 M citric acid, 0.1 mM $Na_2EDTA$, 0.034% sodium octyl sulfate and 25% methanol (pH = 2.75), at a flow rate of 1.0 ml/min. The monoamine and metabolite levels were quantitated using the Dynamax Method Manager software (Rainin, Woburn, MA) with an Apple Macintosh SE computer.

### *[$^3$H]-Paroxetine Binding*

The procedure of Habert et al. (9) as adopted by Battaglia et al. (1) was employed with minor modifications. Briefly, the frontal cortex and hippocampus from one hemisphere were thawed, weighed, and homogenized with a Brinkman polytron (setting 6, 2 × 20 s) in 5 ml of 50 mM Tris HCl containing 120 mM NaCl

TABLE 1B

SUBSTITUTION IN (+)-MBDB-TRAINED ANIMALS

| Drug | Dose (mg/kg; μM/kg) | N* | D† | %SDL‡ | $ED_{50}$§ mg/kg | $ED_{50}$§ μM/kg |
|---|---|---|---|---|---|---|
| PCA | | | | | 0.17¶ (0.10–0.28) | 0.82 (0.50–1.36) |
| PIA | 0.25; 0.84 | 8 | 0 | 25 | 0.54 (0.35–0.82) | 1.81 (1.18–2.74) |
| | 0.50; 1.68 | 9 | 1 | 25 | | |
| | 0.75; 2.52 | 10 | 2 | 63 | | |
| | 1.00; 3.36 | 8 | 0 | 88 | | |
| 5-IAI | 0.25; 0.85 | 9 | 1 | 0 | 0.79 (0.42–1.48) | 2.67 (1.43–5.00) |
| | 0.50; 1.69 | 8 | 0 | 50 | | |
| | 1.00; 3.38 | 10 | 2 | 63 | | |
| | 2.00; 6.77 | 12 | 4 | 75 | | |
| | 2.50; 8.46 | 10 | 2 | 88 | | |

Animals were trained to discriminate either MDMA or (+)-MBDB from saline using a two-lever drug discrimination paradigm. At least eight rats were tested at each dose as indicated. The $ED_{50}$ values for substitution in MDMA-trained (Table 1A) and (+)-MBDB-trained (Table 1B) animals were calculated according to the method of Litchfield and Wilcoxon (12).

*N = Total number of rats tested.

†D = Number of disruptions (50 presses not completed in 5 min).

‡Percentage of responding (N − D) rats selecting the drug lever.

§95% confidence limits in parentheses.

¶Values taken from Johnson et al. (11).

and 5 mM KCl (pH = 7.4). The homogenates were centrifuged at 30,000 × g for 10 min, and washed in the same buffer and recentrifuged. The resulting pellet was resuspended and chilled on ice until assay.

The binding of a single saturating concentration (1 nM) of [$^3$H]-paroxetine in tissue homogenates was examined. Specific binding was defined as that displaceable with 1 μM fluoxetine. Incubations commenced with the addition of tissue to the buffer described above to give a total volume of 2 ml. The tubes were equilibrated at 24°C for 1 h before filtering through GF/C filters presoaked with 0.05% PEI, using a Brandel Cell Harvestor (Gaithersburg, MD). The tubes were then rapidly washed twice with ice-cold buffer. The filters were allowed to air dry and were then placed in scintillation vials, 10 ml of scintillation cocktail was added, and the vials were allowed to sit overnight before counting at an efficiency of 54%.

TABLE 2

UPTAKE INHIBITION OF [$^3$H]-5-HT

| | $IC_{50}$ (nM) |
|---|---|
| PCA | 184 ± 12 |
| PIA | 82 ± 8* |
| 5-IAI | 241 ± 21† |

The inhibition of [$^3$H]-5-HT uptake was examined in rat brain cortical synaptosomes. The $IC_{50}$ values represent the mean ± S.E.M. of three to four separate experiments. Each experiment utilized 5 or 6 concentrations, run in triplicate, on the linear portion of the dose-response curve.

*Indicates significantly different from PCA ($p<0.05$, ANOVA followed by post hoc comparison).

†Indicates significantly different from PIA ($p<0.05$, ANOVA followed by post hoc comparison).

*Uptake Inhibition of [$^3$H]-5-HT*

The procedure of Steele et al. (19) was employed with minor modifications. Briefly, the whole cortex was homogenized in 15 volumes of 0.32 M sucrose with a glass mortar and motor-driven teflon pestle. The homogenate was then centrifuged at 1000 × g for 10 min at 4°C and the resulting supernatant centrifuged at 17,000 × g for 10 min. The resulting pellet was resuspended in the same volume of sucrose and placed in an ice bath until used.

A 200 μl aliquot of the above tissue homogenate was added to 1.65 ml of $O_2$-saturated Krebs-Henseleit buffer (118 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $KH_2PO_4$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 10 mM glucose, 0.06 mM ascorbic acid and 0.03 mM $Na_2EDTA$), 50 μl drug, and 50 μl pargyline (final concentration, 1 μM). Following a 5-min preincubation at 37°C, [$^3$H]-5-HT was added in 50 μl aliquots to give a final concentration of 10 nM. Tubes were allowed to equilibrate for an additional 5 min at 37°C before cooling in an ice bath. The synaptosomes were collected by filtering through Whatman GF/B filters utilizing a Brandel cell harvestor (Gaithersburg, MD). The filters were washed twice with 5 ml of cold buffer and allowed to air dry before preparing the samples for counting as described above.

*Statistical Analysis*

In drug discrimination experiments, $ED_{50}$ values and 95% confidence intervals were determined from quantal dose-response curves according to the procedure of Litchfield and Wilcoxon (12). The $IC_{50}$ values for uptake inhibition were calculated from a graded dose-response curve by the method of Tallarida and

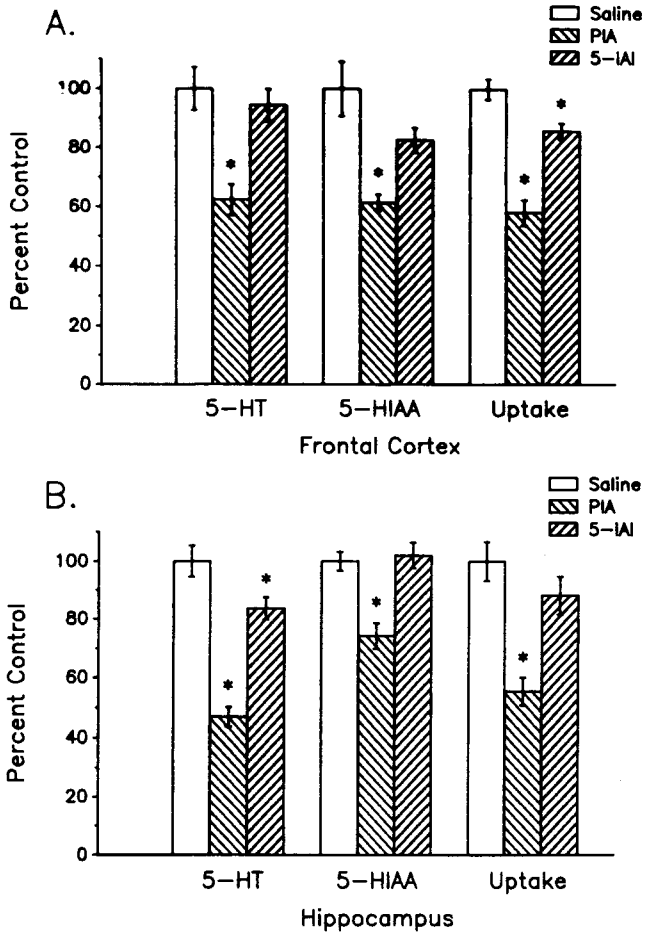


FIG. 2. Serotoninergic markers following acute dosing with PIA or 5-IAI. Saline, 40 mg/kg PIA, or 40 mg/kg 5-IAI was injected subcutaneously and animals were sacrificed one week later. Serotonin and 5-HIAA levels were determined in frontal cortex (A) and hippocampal (B) areas using HPLC-EC techniques. The number of uptake sites remaining was determined by examining the ability of a saturating concentration of [$^3$H]-paroxetine to bind to tissue homogenates as described in the Method section. Values are represented as the mean ± S.E.M. for n = 8. Saline control values were as follows: cortical 5-HT, 366 ± 27; 5-HIAA, 296 ± 27 pg/mg wet wt.; uptake sites, 16.8 ± 0.6 fmol/mg wet wt.; and hippocampal 5-HT, 400 ± 22; 5-HIAA, 558 ± 18 pg/mg wet wt.; uptake sites 16.1 ± 1.1 fmol/mg wet wt.

Murray (20). For neurochemical analyses, comparisons between treatment groups utilized an analysis of variance followed by a post hoc comparison, as embodied in the EPISTAT software (EPISTAT Services, Richardson, TX).

## RESULTS AND DISCUSSION

Both PIA and 5-IAI were behaviorally active in the drug discrimination paradigm. As seen in Table 1, both test compounds fully substituted in rats trained to discriminate MDMA or (+)-MBDB from saline. Interestingly, 5-IAI is significantly less potent than PIA at inhibiting the synaptosomal uptake of [$^3$H]-5-HT in vitro (Table 2). In addition, PIA was significantly less potent than PCA in MDMA-trained rats. Fuller et al. (7) have previously shown that PIA is a less potent depletor of 5-HT and 5-HIAA than is PCA. This occurs despite the fact that PIA has equal or greater potency than PCA in a number of in vitro assays. For example, PIA is slightly more potent than PCA at inhibiting synaptosomal [$^{14}$C]-5-HT uptake (7). In our laboratory, PIA is a significantly more potent inhibitor of synaptosomal uptake of lower concentrations of [$^3$H]-5-HT (Table 2). In addition, Fuller et al. (7) have reported that PIA is substantially more potent than PCA as an inhibitor of monoamine oxidase. Given the similar half-life and distribution of PIA and PCA (7), the reason for the apparent discrepancy between the in vivo and in vitro potencies is not readily apparent.

As seen in Fig. 2, PIA caused a significant decrease in serotonergic markers one week after a single 40 mg/kg (0.13 mmol/kg) dose. This was a selective serotonergic effect since no changes in NE, DA or their metabolites were seen with any drug treatment (Table 3). As previously indicated (7), the relative neurotoxicity of PIA is substantially less than that of PCA. While PCA (0.05 mmol/kg) causes a 75% reduction in serotonergic markers (11), 0.13 mmol/kg of PIA caused only a 40% reduction (Fig. 1). Previously, 0.10 mmol/kg (30 mg/kg) of PIA has been reported to cause a 20 to 30% reduction in 5-hydroxyindoles (7).

As anticipated, 5-IAI appears to be significantly less neurotoxic than PIA (Fig. 2). Only slight decreases of serotonergic markers (15% or less) were seen one week following a single 40 mg/kg (0.13 mM/kg) SC dose of 5-IAI. The only statistically significant decreases were in the number of cortical uptake sites and the hippocampal levels of 5-HT (Fig. 2). One could speculate that higher doses might lead to significant decreases in all the serotonergic parameters. However, a 40 mg/kg dose is already some 20- to 40-fold higher than a behaviorally active dose, and it has been our experience that doses of many amphetamine analogues greater than 40 mg/kg are approaching lethal levels. Interestingly, we have found that similar doses of 6-chloro-2-aminotetralin (0.17 mmol/kg) resulted in slight reductions

TABLE 3

CATECHOLAMINE AND METABOLITE LEVELS

| | Cortical (pg/mg wet wt.) | | | | Hippocampal |
|---|---|---|---|---|---|
| Treatment | NE | DA | DOPAC | HVA | NE |
| Saline | 508 ± 21 | 40 ± 4 | 16 ± 3 | 23 ± 1 | 590 ± 28 |
| PIA | 504 ± 29 | 36 ± 3 | 16 ± 3 | 20 ± 2 | 547 ± 42 |
| 5-IAI | 540 ± 22 | 47 ± 5 | 13 ± 2 | 19 ± 1 | 557 ± 26 |

Saline, 40 mg/kg PIA, or 40 mg/kg 5-IAI was injected subcutaneously and animals were sacrificed one week later. The frontal cortex and hippocampal areas were analyzed for NE, DA, DOPAC, and HVA levels utilizing HPLC-EC techniques. Values are reported as the mean ± S.E.M. for N = 8.

in serotonergic markers at one week, while a statistically significant decrease only occurred with the number of hippocampal 5-HT uptake sites (unpublished results).

In conclusion, the results indicate that both PIA and 5-IAI are behaviorally active in rats. PIA also appears to cause the same type of serotonin neurotoxicity that occurs with PCA, although PIA is somewhat less potent in this respect. Third, at the doses examined, the rigid analogue 5-IAI does not appear to cause significant serotonin deficits in the rat, presumably reflecting a reduced potential to induce serotonin neuron degeneration.

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