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Effect of Acrylamide on Neurotransmitter Metabolism and Neuropeptide Levels in Several Brain Regions and Upon Circulating Hormones

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Abstract. The effect of acute and subchronic acrylamide treatment on levels of dopamine, serotonin, and their metabolites was determined in several brain regions of the rat. Concentrations of several neuropeptides and circulating hormones were also measured. Both a single and repeated doses of acrylamide resulted in elevated levels of 5-hydroxyindolacetic acid in all regions studied (frontal cortex, striatum, hippocampus, brain stem, and hypothalamus). Changes in regional content of other monoamines were much less pronounced. Turnover studies following pargyline blockage of monoamine oxidase, suggested results were due to increased rates of serotonin turnover in acrylamide-treated rats.

Changes in neuropeptide levels were only detected in the hypothalamus where a single acrylamide treatment caused elevated levels of \( \beta \)-endorphin and substance P, and in frontal cortex where met-enkephalin levels were higher after repeated acrylamide injection. Such repeated injection caused a major depression in plasma levels of testosterone and prolactin.

Key words: Acrylamide – Neuroendocrine – Monoamines – Neuropeptides

Introduction

Acrylamide is a commonly used industrial material that has a specific neurotoxic effect. The peripheral nervous system is clearly damaged and both human and experimentally-induced neuropathies have been described (Tilson et al. 1979; Fullerton and Barnes 1966; Fujita et al. 1961). Central nervous system malfunction is also reported for experimental animals and humans (Igisu et al. 1975; Spencer and Schaumburg 1974). Involvement of the sympathetic nervous system has long been suspected (Auld and Bedwell 1967) and recently both the
dopamine and serotonin neuronal circuits have been found abnormal in the brains of acrylamide-treated rats (Agrawal et al. 1981; Agrawal et al. 1981). In addition, changes in prolactin levels of rats exposed to acrylamide suggested that this toxicant might influence neuroendocrine function (Upshouse et al. 1982).

The purpose of the present work was to survey the effects of acrylamide upon monoamine levels in several brain regions. Several other endocrine substances have also been assayed together with neuropeptides thought to modulate neurotransmission. Analysis of neurotransmitter receptors, that are thought to have a reciprocal relationship with the intensity of neurotransmission, was performed. By this means it was hoped to obtain a clearer picture of the effect of acrylamide upon several interrelated neurotransmitter functions.

**Methods**

Eight to 10 week old male Fischer 344 rats were dosed with acrylamide by intraperitoneal injection of an aqueous solution. Dosing consisted of either a single injection of 0, 50, or 100 mg acrylamide/kg body wt. or 10–20 successive daily injections of 0, 10, or 20 mg/kg body wt. in a volume of 2 ml/kg body wt. These doses and time intervals were chosen since they have been previously found to exert relatively selective behavioral and biochemical changes without evidence of gross toxicity such as major loss of body weight (Agrawal et al. 1981a, b; Bondy et al. 1981). Control animals received an equivalent volume of distilled water. Animals were killed by decapitation 24 h after administration of the last dose of acrylamide.

*Estimation of Neuropeptides.* The regional content of met-enkephalin (ME), substance P (SP), neurotensin (NT), and β-endorphin (βE) was determined by radioimmunoassay as has already been described in detail (Hong et al. 1976, 1978). Tissue was homogenized in 2 N acetic acid, then heated to 98° for 5 min, and centrifuged at 25,000 g for 20 min. The supernatant was lyophilized and the residue was reconstituted with H2O and radioimmunoassayed using [tyrosyl-3,5-3H]-met-enkephalin (36 Ci/m mole), 125I-substance P, [tyrosyl-3,5-3H]-neurotensin (61 Ci/m mole) and 125I-β-endorphin (original specific activity of iodine, 65 µCi/µg). Antisera were raised in rabbits using polylysine conjugates. Six injections were given at 2-week intervals before animals were bled. Nonlabeled peptide or brain extract was incubated with antiserum and isotopically-labeled peptides in 0.5 ml of 0.2 M Tris buffer, pH 7.4, containing 0.1% albumin and 0.06% dextran. The incubation was carried out at 4°C for 15–24 h. The labeled peptide bound to antibody was separated from the unbound peptide by adding 0.2 ml of 1.5% charcoal slurry containing 0.15% dextran (suspended in 0.2 M Tris buffer, pH 7.4) and an aliquot of supernatant fluid was counted in a liquid scintillation spectrometer. The specificity of the antisera employed has been previously described (Hong et al. 1978).

*Estimation of Dopamine and Serotonin and Their Metabolites.* The biogenic amine content of various brain regions was assayed by high performance liquid chromatography (HPLC) using the method of Wilson et al. (1982). In brief, tissue was homogenized in 19.3 volumes of chilled 0.1 M HClO4 containing 0.002 M sodium bisulfite. The homogenate was centrifuged (40,000 g 20 min) and the supernatant filtered through 0.2 µm pore size regenerated cellulose filter (Bio-Analytical Systems, Inc., W. Lafayette, IN, USA) prior to chromatography. The filtrate was used for automated analysis of serotonin, dopamine, and their acid metabolites by reversed phase HPLC using an electrochemical detection system. Compounds assayed were dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA). Values of biogenic amine levels were very similar in several regions of control rats, whether they received single or multiple injections of vehicle (distilled water). For this reason control values from singly or repeatedly injected rats were combined, in the case of hippocampus, brain stem, and striatum.
Analysis of Circulating Hormone Levels. Blood was collected from rats at the time of decapitation and after coagulation, was centrifuged at low speed (3,000 g, 10 min). Clear supernatant serum samples were stored at $-70^\circ$ C until assay. Prolactin was measured using a radioimmunoassay kit and reference standards supplied by NIAMDD (Nemeroff et al. 1977). Growth hormone also was estimated using a kit supplied by NIAMDD and testosterone was assayed with a kit from Serono, Braintree, MA.

Pargyline Study. The study involving blockade of monoamine oxidase was carried out in rats 24 h after receiving injections of either water or 100 mg/kg body wt. acrylamide. At this time both sets of rats received 75 mg/kg pargyline a dose sufficient to completely inhibit monoamine oxidase (Tozer et al. 1966) by intraperitoneal injection, and were killed immediately or 30 or 60 min later. HPLC was then carried out in order to determine serotonin and 5-HIAA levels in several brain regions. The basic concept underlying this procedure is that serotonin turnover can be estimated by observing its rate of increase after blockage of its catabolism. The concurrent measurement of the decay rate of the metabolite of serotonin, 5-hydroxyindoleacetic acid can be used to distinguish between altered serotonin turnover and blockage of 5-HIAA efflux through the acid transport mechanism.

Protein Determination. This was carried out using the method of Lowry et al. (1951).

Statistical Analysis. Differences between groups were assessed using Fisher's Least Significant Difference Test after a one-way analysis of variance. The accepted level of significance in all cases was $p < 0.05$ using a two-tailed distribution.

Results

A single injection of acrylamide resulted in a selective but widespread increase in the levels of 5-hydroxyindole acetic acid (5-HIAA) in several brain regions (Table 1). This response tended to be dose-dependent in that it was larger at the higher acrylamide dose (100 mg/kg). The level of serotonin was also significantly elevated in the frontal cortex and brain stem. Levels of dopamine and dihydroxyphenylacetic acid (DOPAC) were not significantly altered in any region studied, at either dose used.

When acrylamide was repeatedly administered over a period of 10 days, similar elevations of 5-HIAA were apparent and in this case serotonin levels were elevated in the frontal cortex of treated rats (Table 2). In addition, dopamine and DOPAC levels were decreased in the frontal cortex, a region where their normal levels are low.

The inhibition of monoamine oxidase by pargyline, progressively increased 5-HT levels and decreased 5-HIAA levels in the striatum (Fig. 1). The rate of decline of 5-HIAA in acrylamide-treated rats, although starting from a higher initial levels, roughly paralleled that of control rats. The $t_{1/2}$ of 5-HIAA was 82 min in the striatum of control rats and 71 min in acrylamide-treated rats. The turnover rate of serotonin derived from the steady state level divided by the half-life of its catabolite 5-HIAA (Tozer et al. 1966) was dramatically increased in the striatum of acrylamide-treated rats. The rate of serotonin catabolism was 0.27 µg/g wet tissue/h in control and 0.67 µg/g tissue/h in experimental animals. This large increase in turnover rate was not found in all regions. For example the corresponding hypothalamic values were 0.54 µg/g wet tissue/h for control and 0.74 µg/g tissue/h for experimental animals.
### Table 1. Effect of a single administration of acrylamide on levels of biogenic amines in various brain areas

| Acrylamide dose (mg/kg body wt.) | µg/g wet tissue | Dopamine | DOPAC        | Homovanillic acid | Serotonin | 5-HIAA   |
|----------------------------------|----------------|----------|--------------|-------------------|-----------|----------|
|                                  |                |          |              |                   |           |          |
| Frontal cortex                   |                |          |              |                   |           |          |
| 0                                | 0.10 ± 0.01    | 0.44 ± 0.01| 0.44 ± 0.02  |                   |           |          |
| 50                               | 0.11 ± 0.01    | 0.46 ± 0.01| 0.59 ± 0.03* |                   |           |          |
| 100                              | 0.11 ± 0.02    | 0.53 ± 0.01*| 0.63 ± 0.02* |                   |           |          |
| Striatum                         |                |          |              |                   |           |          |
| 0                                | 10.0 ± 0.3     | 1.12 ± 0.05| 0.87 ± 0.04  | 0.63 ± 0.01       | 0.73 ± 0.05|          |
| 50                               | 9.4 ± 0.3      | 1.10 ± 0.05| 1.01 ± 0.06  | 0.65 ± 0.03       | 1.27 ± 0.05*|          |
| 100                              | 9.6 ± 0.4      | 1.11 ± 0.05| 1.08 ± 0.07* | 0.69 ± 0.04       | 1.43 ± 0.04*|          |
| Hippocampus                      |                |          |              |                   |           |          |
| 0                                |                | 0.75 ± 0.02| 0.66 ± 0.02  |                   |           |          |
| 50                               |                | 0.80 ± 0.03| 1.14 ± 0.06* |                   |           |          |
| 100                              |                | 0.80 ± 0.04| 1.07 ± 0.04* |                   |           |          |
| Brain stem                       |                |          |              |                   |           |          |
| 0                                |                | 0.80 ± 0.02| 0.69 ± 0.04  |                   |           |          |
| 50                               |                | 0.85 ± 0.02| 0.93 ± 0.03* |                   |           |          |
| 100                              |                | 0.94 ± 0.03*| 1.18 ± 0.05* |                   |           |          |

Each value represents a mean derived from six to eight animals, together with the standard error. *p < 0.05 that value differs from corresponding zero-dose (Fisher's Least Significant Difference Test).

### Table 2. Effect of 10 days repeated administration of acrylamide on levels of biogenic amines in various brain areas

| Brain region | µg/g wet tissue | Dopamine | DOPAC        | Homovanillic acid | Serotonin | 5-HIAA   |
|--------------|----------------|----------|--------------|-------------------|-----------|----------|
|              |                |          |              |                   |           |          |
| Frontal cortex|                |          |              |                   |           |          |
| C            | 0.16 ± 0.02    | 0.08 ± 0.01| 0.09 ± 0.01  | 0.54 ± 0.01       | 0.47 ± 0.01|          |
| E            | 0.11 ± 0.01*   | 0.06 ± 0.003*| 0.10 ± 0.01  | 0.64 ± 0.02*      | 0.72 ± 0.02*|          |
| Striatum     |                |          |              |                   |           |          |
| C            | 10.0 ± 0.3     | 1.12 ± 0.05| 0.87 ± 0.04  | 0.63 ± 0.01       | 0.73 ± 0.05|          |
| E            | 10.3 ± 0.4     | 1.06 ± 0.05| 0.83 ± 0.07  | 0.68 ± 0.02       | 0.98 ± 0.02*|          |
| Hippocampus  |                |          |              |                   |           |          |
| C            | 0.75 ± 0.02    | 0.66 ± 0.02|              |                   |           |          |
| E            | 0.82 ± 0.04    | 0.89 ± 0.03*|             |                   |           |          |
| Brain stem   |                |          |              |                   |           |          |
| C            | 0.80 ± 0.09    | 0.69 ± 0.13|              |                   |           |          |
| E            | 0.90 ± 0.04    | 0.83 ± 0.10*|             |                   |           |          |
| Hypothalamus |                |          |              |                   |           |          |
| C            | 0.38 ± 0.03    | 0.94 ± 0.02| 0.72 ± 0.01  |                   |           |          |
| E            | 0.35 ± 0.01    | 1.08 ± 0.03| 0.96 ± 0.01* |                   |           |          |

Each value represents a mean derived from six to eight animals, together with the standard error. *p < 0.05 that experimental value (E) differs from control (C) using Fisher's Least Significant Difference Test. Experimental animals received 10 daily injections of acrylamide (10 mg/kg body wt.)
Fig. 1. Levels of striatal serotonin and 5-HIAA of acrylamide-treated and control rats after pargyline administration. Each point represents a mean ± SE derived from five rats at various intervals after intraperitoneal injection of pargyline (75 mg/kg body wt.). Experimental rats received 100 mg/kg body wt. acrylamide 24 h prior to pargyline injection. (○) serotonin in control rats; (△) 5-HIAA in control rats; (●) serotonin in acrylamide-dosed rats; (▲) 5-HIAA in acrylamide-dosed rats.

Table 3. Neuropeptide levels in various brain areas 24 h after a single administration of acrylamide

| Acrylamide dose (mg/kg) | Peptide content (ng/10 mg wet wt.) |
|------------------------|----------------------------------|
|                        | Met-enkephalin | Neurotensin | β-Endorphin | Substance P |
| Frontal cortex         |                 |             |             |             |
| 0                      | 0.34 ± 0.04     | 0.21 ± 0.02 | 0.23 ± 0.01 | 0.16 ± 0.01 |
| 50                     | 0.32 ± 0.03     | 0.23 ± 0.01 |             |             |
| 100                    | 0.23 ± 0.03     |             |             |             |
| Striatum               |                 |             |             |             |
| 0                      | 20.0 ± 0.7      | 0.26 ± 0.05 | 3.8 ± 0.2   |             |
| 50                     | 17.5 ± 1.7      | 0.15 ± 0.03*| 3.7 ± 0.1   |             |
| 100                    | 18.2 ± 0.3      | 0.28 ± 0.07 | 4.0 ± 0.1   |             |
| Brain stem             |                 |             |             |             |
| 0                      | 0.28 ± 0.03     | 5.1 ± 0.2   |             |             |
| 50                     | 0.26 ± 0.02     | 5.3 ± 0.3   |             |             |
| 100                    | 0.28 ± 0.01     | 5.1 ± 0.3   |             |             |
| Hypothalamus           |                 |             |             |             |
| 0                      | 7.1 ± 0.4       | 1.7 ± 0.1   | 6.9 ± 0.6   |             |
| 50                     | 7.5 ± 0.2       | 1.7 ± 0.1   | 7.3 ± 0.7   |             |
| 100                    | 7.8 ± 0.5       | 1.9 ± 0.1   | 8.6 ± 0.6*  |             |

Each value represents a mean derived from six to eight animals, together with the standard error *p < 0.05 that the experimental value differs from the corresponding control (Fisher's Least Significant Difference Test).

Changes in neuropeptide levels observed 24 h after a single injection of acrylamide were largely confined to the hypothalamus (Table 3). Acrylamide significantly elevated β-endorphin and substance P in this area while levels of met-enkephalin and neurotensin were unaltered. However, striatal neurotensin was decreased at the lower, but not the higher, acrylamide dose (Table 3). After repeated dosing with the same regimen as that used in the monoamine level studies, (10 days of 10 mg/kg acrylamide body wt. daily), neuropeptide levels were unchanged from control values (data not shown). For this reason the
Table 4. Effect of repeated acrylamide administration on levels of neuropeptides within several brain regions

| Daily acrylamide Dose (mg/kg body wt.) | Peptide content (ng/10 mg wet wt.) | Met-enkephalin | Neurotensin | β-Endorphin | Substance P |
|----------------------------------------|------------------------------------|----------------|-------------|-------------|-------------|
| Frontal cortex                          |                                    |                |             |             |             |
| 0                                      | 0.34 ± 0.04                        |                |             | 0.21 ± 0.02 |             |
| 10                                     | 0.46 ± 0.03                        |                |             | 0.20 ± 0.02 |             |
| 20                                     | 0.53 ± 0.04*                       |                |             | 0.25 ± 0.03 |             |
| Striatum                               |                                    |                |             |             |             |
| 0                                      | 15.3 ± 0.6                         | 0.33 ± 0.02    |             | 2.00 ± 0.04 |             |
| 10                                     | 15.0 ± 0.3                         | 0.33 ± 0.01    |             | 2.03 ± 0.13 |             |
| 20                                     | 15.4 ± 0.3                         | 0.32 ± 0.01    |             | 2.12 ± 0.09 |             |
| Brain stem                             |                                    |                |             |             |             |
| 0                                      | 1.58 ± 0.03                        | 0.47 ± 0.02    |             |             |             |
| 10                                     | 1.63 ± 0.04                        | 0.47 ± 0.02    |             |             |             |
| 20                                     | 1.52 ± 0.03                        | 0.42 ± 0.02    |             |             |             |
| Hypothalamus                           |                                    |                |             |             |             |
| 0                                      | 6.1 ± 0.2                          | 2.8 ± 0.3      | 2.8 ± 0.3   | 7.2 ± 0.3   |             |
| 10                                     | 5.4 ± 0.4                          | 2.6 ± 0.2      | 2.8 ± 0.4   | 6.5 ± 0.5   |             |
| 20                                     | 5.5 ± 0.3                          | 2.6 ± 0.2      | 2.3 ± 0.3   | 7.4 ± 0.3   |             |

Values are means derived from six to eight rats dosed with acrylamide for 20 successive days. *p < 0.005 that value differs from corresponding zero dose (Fisher’s Least Significant Difference Test).

Table 5. Levels of circulating hormones in male rats after repeated administration of acrylamide

| Hormone          | Acrylamide dose (mg/kg daily) | 0     | 10    | 20    |
|------------------|------------------------------|-------|-------|-------|
| Testosterone     |                              | 2.13 ± 0.44 | 1.65 ± 0.60 | 1.02 ± 0.16* |
| Growth hormone   |                              | 11.1 ± 3.2   | 19.8 ± 7.7   | 17.7 ± 2.1   |
| Prolactin        |                              | 27.9 ± 12.4  | 8.1 ± 3.2    | 5.2 ± 1.9*   |

Male rats were treated with daily injections of acrylamide for 20 days. Data are mean ± SE of results from five to eight animals and are expressed as ng/ml serum. *p < 0.05 that value differs from control (Fisher’s Least Significant Difference Test).

Period of dosing was extended to 20 days and the level of daily dosing was increased to 20 mg/kg body wt. Even at this level, only one significant change in a neuropeptide concentration was apparent (Table 4). The level of frontal cortical met-enkephalin was increased and this increase was very significant (p < 0.005).

Values for circulating hormones were determined in serum derived from rats receiving 20 daily injections of acrylamide (10 and 20 mg/kg body wt.). A dose-dependent depression of testosterone and prolactin levels was found while growth hormone levels were not significantly different from control levels (Table 5).
Neurotoxicity of Acrylamide

Discussion

The results obtained in this work indicate an unusually broad serotonergic response to acrylamide. The widespread elevated levels of 5-HIAA caused by this toxicant suggest an increased turnover of serotonin reflecting elevation of serotonergic activity. Earlier work implicated dopaminergic pathways and sympathetic activation as a major effect of acrylamide (Agrawal et al. 1981; Bondy et al. 1981a; Auld and Bedwell 1967). This is consistent with the small but significant changes observed in levels of DA, DOPAC, and HVA found in some brain regions of treated animals. The present data imply that serotonin neurons are also affected. Both single and repeated doses of acrylamide in our earlier work, however, showed alterations of serotonin receptors in the frontal cortex (Agrawal et al. 1981).

The finding that the rate of decrease of 5-HIAA levels following pargyline treatment was very similar in acrylamide-treated rats and in control rats, suggested that the elevated 5-HIAA level in acrylamide-treated rats was due to an increased rate of serotonin catabolism rather than a reduced rate of 5-HIAA efflux (Tozer et al. 1966; Sharpless 1981). There was no clear regional heterogeneity of response of 5-HIAA levels to acrylamide. A recent report (Dixit et al. 1981) using an acrylamide dosing schedule similar to that reported here, indicated a widespread depression of catecholamines and serotonin. However, these authors used a fluorimetric assay method which yielded basal values for dopamine and serotonin greatly in excess of generally reported values (Thierry et al. 1973; Moore et al. 1978; Saavedra 1977).

The elevated $\beta$-endorphin levels in the hypothalamus may reflect relative inactivity of $\beta$-endorphin-containing neurons and this may be due to the greater inhibitory influence of active serotonin neurons (Van Loon and De Souza 1978). Interaction of opiate and serotonergic systems is suggested by the finding that morphine treatment may enhance serotonergic activity in the brain stem of rats (Mennini et al. 1981). Morphine can also increase the rate of release of serotonin in the hindbrain (Pycock et al. 1981). Increased concentrations of serotonin and 5-HIAA have been found after exposure of animals to chlordecone (Fujimori et al. 1981; Hong and Wilson, unpublished data), and it may be that serotonergic neurons are especially sensitive to a variety of organic neurotoxicants and this is expressed by their hyperactivity.

Another generalization that this report supports, is that circulating testosterone levels are depressed by a variety of neurotoxicants including manganese and chlordecone (Hong et al. unpublished data) and lead (Braunstein et al. 1978). Reduced levels of prolactin and testosterone may imply a reduced responsivity of these hormones to environmental stimuli (Frankel 1981). A single administration of acrylamide at a relatively high dose is also sufficient to reduce prolactin levels (Uphouse et al. 1982). Since serotonin has been reported to elevate prolactin levels (Frohman 1980), the increased serotonin turnover and the depressed prolactin levels reported here are likely to be independent phenomena. It is also difficult to relate the transient response of two hypothalamic neuropeptides to the prolonged disruption to the hypothalamic-pituitary-endocrine axis that acrylamide appears to cause. It may be that
some circuits have a greater ability to overcome neurotoxically-induced derangement than others.

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