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NEUROTOXIC INDOLEAMINES AND MONOAMINE NEURONS[1]

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H. G. Baumgarten
Department of Neuroanatomy, University of Hamburg, Hamburg, German Federal Republic

A. Björklund
Department of Histology, University of Lund, Lund, Sweden

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INTRODUCTION

In 1968 Thoenen & Tranzer (1) discovered that the long-lasting depletion of NA in sympathetically innervated organs by 6-OH-DA is due to degeneration of NA terminals. This provided the basis for the development of a new concept in neurobiological research: the method of selective chemical neurodegeneration. The successful application of this method to produce degeneration of DA and NA neurons in brain (2, 3) stimulated a search for compounds with comparable effects on central 5-HT neurons. In studies with a restricted number of 5-HT analogs, we were able to show that certain dihydroxylated tryptamines caused toxic damage to serotonin terminals. The recent findings by Björklund, Baumgarten & Rensch (4) and Gerson & Baldessarini (5) that DMI treatment prior to intraventricular 5,7-DHT injection prevents the damaging effect of the latter drug on NA but not on 5-HT neurons indicate that powerful and probably rather selective destruction of central indoleamine–containing axons and terminals can be achieved.

BIOCHEMICAL EFFECTS

Effects on Monoamine Levels

Table 1 depicts those tryptamines that have been found to cause substantial long-term depletion of 5-HT in the brain and spinal cord (6, 7). A standard dose of 50 μg free-base 5,6-DHT, 5,7-DHT, N-m-5,6-DHT, N-m-5,7-DHT, or 5,6-DAcOT

[1]Abbreviations used: CA, catecholamine(s); DA, dopamine; 5,6-DAcOT, 5,6-diacetoxytryptamine; DHT, dihydroxytryptamine(s); DMI, desmethylimipramine; 5-HIAA, 5-hydroxyindole acetic acid; HT, hydroxytryptamine(s); IC, inhibitory concentration; 6-OH-DA, 6-hydroxydopamine; MAO, monoamine oxidase; NA, noradrenaline; N-m-, N-methyl-.

Table 1 Effects of five potent neurotoxic indoleamines on whole brain and spinal cord serotonin and catecholamine content[a,b]

	5-HT content (% control)		NA content (% control)		DA content (% control)
	Brain	Spinal cord	Brain	Spinal cord	Brain
5,6-DHT (50 μg)	56	12	84	121	70
5,6-DAcOT (50 μg)	59	21	117	158	93
N-m-5,6-DHT (50 μg)	76	24	104	115	98
5,7-DHT (50 μg)	48	12	52	42	91
5,7-DHT (150 μg)	17	10	48	16	*[c]
5,7-DHT (150 μg) + + DMI (25 mg/kg)	21	10	124	95	*[c]
N-m-5,7-DHT (50 μg)	63	16	65	68	90

[a] Each drug (calculated as the free-base) was given in a single intraventricular injection (student's *t*-test).

[b] Data from references 4, 6, and 8.

[c] *, not assayed.

results in a 25 to 50% reduction of brain 5-HT and a loss of 80–90% of 5-HT from the spinal cord 8–12 days after injection. Other mono- or dihydroxylated indoleamines, including the α-methylated derivatives of 5,6- and 5,7-DHT, were found to be less efficient long-term depletors of brain 5-HT. All nonsubstituted DHTs tested (5,6-, 5,7-, 4,5-, and 6,7-DHT) also decrease brain CA levels, indicating a relative nonselectivity in the action of these compounds (6,7). While 6,7- and 4,5-DHT deplete NA even more efficiently than 5-HT (6,7), 5,7-DHT (in doses up to 75 μg) has similar depleting effects on NA and 5-HT in the brain (8,9). Besides its strong depleting action on brain and spinal cord 5-HT, 5,6-DHT produces marginal, though significant, long-term reductions of both NA and DA in brain (16 and 30% reduction, respectively, at 8–12 days after 50 μg 5,6-DHT; references 6, 7). The acetic acid ester derivative of 5,6-DHT, 5,6-DAcOT, is more specific than 5,6-DHT when given in doses up to 50 μg (6). Increasing the dose of 5,6-DAcOT fails to enhance its long-term action on brain 5-HT but tends to impair its selectivity for 5-HT neurons.

The long-term effect of 5,6-DHT on brain 5-HT is maximal after a dose of 50–75 μg (free base). Increasing the dose above 75 μg fails to cause any further reduction in 5-HT, but results in enhancement of its nonspecific toxic effects as well as in increased depletion of brain CA (10, 11). 5,7-DHT depletes brain 5-HT in a dose-related manner up to a dose of about 200 μg (8), and this is true also for spinal cord NA. By contrast, the depletion of NA in the brain is maximal already after 50 μg. From fluorescence histochemical observations it seems likely that this latter phenomenon is due to a failure of 5,7-DHT to penetrate to NA fiber systems remote from the ventricles in sufficiently high concentrations to produce toxic damage. Thus, after 50 μg, there is, in the brain, a zone of efficient damage to NA axons of about 1 to 2 mm from the ventricular surface, and this zone does not increase appreciably at higher doses of 5,7-DHT (12).

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Time-course analysis of the 5-HT depletion pattern following 5,6- or 5,7-DHT reveals that minimum amine levels are not reached until 4 to 12 days after drug injection in some brain regions and in the spinal cord (9, 11). This points to the importance of anterograde degeneration of nerve terminals following primary lesions to the nonterminal axons as an important mechanism of damage in the central 5-HT neurons (8, 9, 11, 13). Generally, the reduction in 5-HT levels is smallest in cell body–rich CNS regions, which reflects the resistance of the neuronal pericarya to the acute toxic effects of 5,6- or 5,7-DHT (see below).

It has been shown that the extent and specificity of 5-HT depletion in the adult rat brain by 5,6-DHT depends on the route of administration, the speed of injection, and the type of anesthesia used (10). Generally, intracisternal injections yield less 5-HT depletion than intraventricular ones (14–17). This difference is greater the more autoxidizable the drug. Thus, larger differences are noted with 5,6-DHT, which is more rapidly autoxidized, than with 5,7-DHT. Low doses of 5,7-DHT, when administered intracisternally in newborn rats, have been found to cause long-lasting, profound reductions in CNS 5-HT and 5-HIAA with little effect on brain NA (19). These findings indicate that the intracisternal route of administration is very useful in developing animals, probably because of the relatively large size of the ventricular system, facilitating rapid distribution of the drug in the cerebrospinal fluid and efficient penetration into the small brain.

As shown by Björklund et al (18) the neurotoxic indoleamines are highly suitable for direct intracerebral administration by local stereotaxic injection of small amounts of the drugs. This offers a very useful tool for localized selective lesioning of 5-HT-containing axon bundles or terminal systems. The intracerebral route of administration may also help to circumvent problems of nonselectivity and general toxicity encountered after intraventricular or intracisternal injections (for discussion, see references 9 and 18).

Uptake Site Affinity

Table 2 compares, for the five most potent neurotoxic tryptamines, the IC-50 values for the inhibition of the uptake of ^{3}H-5-HT into brain homogenates, with the relative percentage inhibition of ^{3}H-5-HT, ^{3}H-NA, and ^{3}H-DA uptake, measured at fixed concentrations of the tryptamines (20, 21). Two compounds, N-methyl-5,6-DHT and 5,6-DHT, have affinities to the 5-HT uptake system close to 5-HT itself. (IC-50 for 5-HT, 10^{-7} M; for 5,6-DHT, 6.0×10^{-7} M; for N-methyl-5,6-DHT, 3.7×10^{-7} M). 5,7-DHT is approximately 7 times weaker as an inhibitor of 5-HT transport than 5,6-DHT (20, 21). The IC-50 of 5,7-DHT indicates, however, that this compound competes more successfully for the 5-HT uptake sites than does 6-OH-DA for the NA or DA uptake sites (22). As revealed by the studies referred to earlier, the uptake of 5,7-DHT into noradrenergic neurons can be counteracted by pretreatment with the potent inhibitor of NA uptake, DMI, thereby improving its selectivity of action on 5-HT neurons (4, 5). Similarly, it has been reported that side effects of 5,6-DHT can be counteracted, and its selectivity increased by DMI (23). It is evident from these findings that the uptake of neurotoxic indoleamines is mediated by the same transport mechanism that mediates reuptake of the natural transmitter.

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Table 2 Uptake site affinity and neurotoxic potency of five neurotoxic indoleamines, as evaluated in vitro[a]

	Affinity for 5-HT uptake sites[b]	Percentage inhibition of uptake[c]			In vitro toxicity at 10^{-6} M[d]	
		5-HT	NA	DA	^{3}H-5-HT uptake (% reduction)	^{3}H-NA uptake (% reduction)
5,6-DHT	6.0×10^{-7} M	59.0 (1 μM)	43.3 (1 μM)	44.7 (1 μM)	-57	+9
5,6-DAcOT	7.4×10^{-5} M	53.9 (10 μM)	23.0 (10 μM)	31.6 (10 μM)	-48	-11
N-methyl-5,6-DHT	3.7×10^{-7} M	72.3 (1 μM)	39.1 (1 μM)	37.4 (1 μM)	-64	-26
5,7-DHT	4.0×10^{-6} M	27.5 (1 μM)	32.5 (1 μM)	15.4 (1 μM)	-65	-24
N-methyl-5,7-DHT					-63	-18

[a] Data from reference 21.

[b] Measured as the concentration of the compound causing 50% inhibition of the ^{3}H-5-HT uptake by synaptosomes prepared from rat hypothalamus.

[c] Measured in synaptosomes from rat hypothalamus (^{3}H-5-HT and ^{3}H-NA) or striatum (^{3}H-DA). The inhibition was measured at a fixed concentration of the added compound (10^{-6} or 10^{-7} M).

[d] Measured in thin cortical slices as the effect of a 30 min incubation at +37°C (in the presence of 10^{-6} M of the various compounds) on the uptake of ^{3}H-5-HT (0.5×10^{-7} M) or ^{3}H-NA (10^{-7} M) during a subsequent incubation for 10 min.

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Impairment of Amine Uptake In Vitro

Reduction in the capacity of the tissue to accumulate tritiated amines is an early and sensitive sign of axonal damage in monoaminergic neurons. We have taken advantage of this fact in a series of in vitro studies in which the tissue was preincubated with the neurotoxic indoleamines at concentrations of 10^{-7} to 10^{-5} M for up to 60 min. After thorough rinsing of the tissue, the ^{3}H-5-HT or ^{3}H-NA uptake capacity was then measured in a subsequent 10 min incubation (21). The extent of reduction in ^{3}H-amine uptake measured in this way is considered to reflect the "neurotoxic potency" of the indoleamine analyzed. Monohydroxylated tryptamines, such as 4-HT, 5-HT, 6-HT, and 7-HT do not cause uptake impairment under these conditions, whereas all dihydroxylated analogs (4,5-DHT, 5,6-DHT, 5,7-DHT, and 6,7-DHT, as well as the N-methylated derivatives of 5,6- and 5,7-DHT) are active (Table 2). 5,6-, 5,7-DHT, and their N-methylated analogs are the most potent compounds. Maximum impairment in ^{3}H-5-HT uptake (60-65% reduction after a 30 min exposure to the drugs) is obtained at 10^{-6}M, and the effect is almost negligible with 10^{-7}M. This suggests that their toxicity depends on reaching a critical concentration. At the same time, these experiments demonstrate that the neurotoxicity develops rapidly: a 5 min exposure to 10^{-5}M 5,6-DHT, followed by a 20 min rinsing in buffer, is sufficient to produce maximum impairment of the subsequent ^{3}H-5-HT uptake. From a comparison with the data of Sachs (24) on the in vitro effects of 6-OH-DA it is evident that the concentrations of the 5,6- or 5,7-DHTs required to produce damage to serotonin terminals in vitro are much lower than the concentrations of 6-OH-DA required to produce damage to CA terminals. This points to a high intrinsic neurotoxic potency of the hydroxylated indoleamines.

Reduction in ^{3}H-Amine Uptake In Vivo

It is generally believed that the uptake of ^{3}H-amines into brain slices or homogenates is related to the amount of intact monoaminergic nerve terminals in the tissue. Therefore, the extent of terminal degeneration induced by treatment with neurotoxic amines can be evaluated by measuring ^{3}H-amine uptake at various intervals after drug administration. Such measurements have been performed at 8–14 days after intraventricular 5,6-, 5,7-DHT, or 5,6-DAcOT (6, 8, 9, 25). The reduction of ^{3}H-5-HT and ^{3}H-NA uptake induced by these compounds parallels fairly well the percentage depletion of endogenous 5-HT and NA, strongly supporting the idea that these compounds cause axonal degeneration of monoamine neurons in brain and spinal cord.

Effects on Enzymes of Monoamine Biosynthesis

In the CNS, tryptophan hydroxylase is supposed to be selectively confined to 5-HT neurons (26). Activities of this enzyme following administration of 5,6- or 5,7-DHT may, therefore, reflect the functional state of the neurons in response to a chemical injury. A complicated, mostly biphasic, depletion and recovery pattern is disclosed in many CNS regions after 5,6-DHT treatment (27). These changes can be interpreted as an initial, direct enzyme inactivation, a subsequent loss of activity due to

direct terminal degeneration, an intermediate rise of enzyme activity due to increased pericaryal synthesis, and finally, a retarded loss of activity due to anterograde loss of terminals. A further long-term recovery of enzyme in some regions is consistent with the idea of functional recovery and/or axonal regeneration in the central 5-HT systems (28–30). A dramatic reduction of tryptophan hydroxylase is seen after 5,7-DHT in the adult rat (31) concomitant with a slight reduction in regional dopamine-β-hydroxylase, but not tyrosine hydroxylase activity (32), in accordance with the unselective effect of 5,7-DHT on NA neurons. The unchanged activity of tyrosine hydroxylase in all forebrain regions analyzed is thought to reflect the integrity of the dopaminergic neurons. Similar findings have been obtained in developing rats (33).

MORPHOLOGICAL EFFECTS

Central Nervous System

Shortly after the intraventricular injection of 5,6-DHT, an indoleamine fluorophore (induced by 5,6-DHT itself) can be visualized that is preferentially confined to monoaminergic axons, terminals, and cell bodies, provided they have a ventricle-near location. The 5,6-DHT fluorophore is no longer detectable in these monoaminergic fibers after 24 hr. By this time, the indoleamine axons have developed signs of damage, that is, numerous grotesque enlargements resembling axonal dilatations after mechanical injury (9, 13, 18, 25, 34, 35). Concomitantly, there is a loss of many ventricle-near indoleamine terminals. Additional indoleamine terminals, not acutely affected by 5,6-DHT, disappear from brain after a latency of four days or more, reflecting anterograde degeneration processes. Although no acute toxic effects of 5,6-DHT on cell bodies have been demonstrated, some pericarya disintegrate by retrograde injury (13, 36). A few days after 5,6-DHT injection, sprouting of indoleamine axons is noted in the vicinity of the drug-damaged axonal stumps. These sprouting fibers regrow during the subsequent months (see section on regeneration of the drug-lesioned central neurons).

In principle, 5,7-DHT produces similar pathological changes in central 5-HT neurons as 5,6-DHT does but, in addition, 5,7-DHT damages NA axons and terminals (8, 18, 35–37). Even after moderate intraventricular doses, 5,6-DHT causes bilaterally a reduction in the number of ventricle-near DA terminals of the caudate whereas the NA systems seem morphologically intact (25).

Terminal degeneration and axonal injury induced by 5,6-DHT have been observed in the electron microscope. In addition, it has been shown that 5,6-DHT is capable of unselectively damaging myelinated axons (38). 5,7-DHT seems to be largely devoid of such unspecific toxic side effects (35).

Peripheral Nervous System

A partial chemical axotomy of sympathetic adrenergic neurons can be achieved by high doses of 5,6-DHT in combination with MAO inhibition (39). To prevent the animals from getting severe cardiovascular side effects (a 5-HT-like intense vasoconstriction), α-adreno receptor and 5-HT receptor blockers have to be administered before intravenous or intraperitoneal 5,6-DHT injections. 5,7-DHT is, on the other

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hand, well tolerated in doses up to 60 mg/kg and causes degeneration of NA terminals in many target organs (40). Its potency on peripheral sympathetic neurons, at the 60 mg/kg dose level, resembles that of 6-OH-DA.

REGENERATION OF THE DRUG-LESIONED CENTRAL NEURONS

Following the initial lesion of the serotonin systems by an intraventricular dose of 75 μg 5,6-DHT, and to a lesser extent after 150 μg 5,7-DHT, there is a regrowth of the damaged axons during the subsequent months. After 5,6-DHT this is reflected in a significant recovery of 5-HT in all regions analyzed, except the spinal cord, between 1 and 6 months (28–30). Separate analysis of lower and higher segments of the spinal cord has shown that a significant recovery of the 5-HT levels occurs also in most cranial spinal cord segments. This is paralleled by an extensive development of new, sprouting indoleamine fibers, as visualized in the fluorescence microscope (28, 29, 36), and by a recovery of the ^{3}H-5-HT uptake capacity in several brain regions (28). The fluorescence histochemical analysis of the 5,6-DHT-treated animals has revealed that the regenerating axons are able to partly regrow to their original terminal areas. In addition, apparently abnormal fiber patterns are formed in many regions where no or only few indoleamine-containing fibers can be detected normally; in still other areas, normally supplied with indoleaminergic fibers, there is an overgrowth of 5-HT axons leading to a hyperinnervation (28, 29, 36).

Regeneration in the serotonin systems occurs also after a high dose of 5,7-DHT but is more restricted than after 5,6-DHT and primarily confined to the lower brain stem (36). This difference has been explained by the fact that the high dose of 5,7-DHT produces lesions in the indoleamine axons that lie closer to the cell bodies, resulting in a higher incidence of retrograde cell loss and in an impaired regeneration. The most active and extensive regeneration after 5,7-DHT takes place in the NA systems (12, 37, 41). Thus, many diencephalic and telencephalic centers initially denervated by the drug treatment are efficiently reinnervated by the regrowing, sprouting NA fibers. This is accompanied by a recovery of brain NA levels and ^{3}H-NA uptake (12, 37).

The regrowth phenomena in the 5,6- and 5,7-DHT-lesioned neurons have to be taken into consideration when interpreting behavioral or functional data in treated animals. It is highly probable that the regenerated fibers reestablish synaptic contacts, either in the initially denervated areas or in abnormal sites, and these may well be of critical importance for recovery of function in the lesioned animals. A detailed knowledge of the degeneration-regeneration processes is obviously necessary for an understanding of the functional consequences of a neurotoxic lesion.

THE USE OF DRUGS FOR MODIFYING THE ACTIONS OF NEUROTOXIC INDOLEAMINES

Because of the small difference in their affinity to the 5-HT and CA uptake sites (see section on uptake site affinity), almost all neurotoxic indoleamines tested cause

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unselective damage to CA neurons in addition to their effects on 5-HT neurons. Among the several possibilities for improving their specificity of action against CNS indoleamine neurons two methods have been found satisfactory: (*a*) interference with the unspecific uptake of 5,6- or 5,7-DHT into CA neurons by inhibitors of catecholamine transport, such as DMI (4, 5, 23, 41), and (*b*) counteraction of the toxic effects of 5,7-DHT on central NA neurons by prior monoamine oxidase inhibition (41, 42). Such combined treatments thus render 5,7-DHT a tool for powerful, long-lasting, and remarkably selective degeneration of 5-HT neurons in the rat CNS.

BEHAVIORAL AND NEUROENDOCRINE EFFECTS

Intraventricular 5,6- or 5,7-DHT injections, when given alone or in combination with DMI, produce characteristic behavioral alterations in adult male rats, consisting of transitory deficits in themoregulation; persistent increases in irritability; hyperresponsiveness and failure to adapt to tactile, optic, acoustic, and pain stimuli; hypersexuality; enhanced aggressiveness and bizarre social interaction; and changes in sleep pattern and cortical EEG (10, 15, 17, 41, 43). Similar though much less dramatic behavioral disturbances have been documented after *p*-chlorophenylalanine, a well-established, long-lasting inhibitor of tryptophan hydroxylase (44), and may thus reflect interference with serotonergic transmission in brain.

The effects induced by selective degeneration of 5-HT axons and terminals in brain have gained particular interest for the elucidation of the role of serotonergic neurons in the control of secretion of anterior pituitary hormones. The results obtained with 5,7-DHT suggest a serotonergic inhibitory control of serum growth hormone levels in the developing male and female rat, but no clear role in the adult rat (45, 46). The findings in developing animals are, however, complicated by the strong, though transitory, anorexigenic effects of neonatally administered 5,7-DHT. Other recent data obtained with 5,7-DHT suggest that contrary to published concepts serotonergic neurons may furnish stimulatory inputs to LH secretion, as judged from the depression of serum LH in adult male rats following treatment with DMI plus 5,7-DHT (47). Serotonin appears also to be involved in the inhibition of the pituitary release of prolactin in the adult male rat (47). The specificity of this latter effect is, however, difficult to assess, since serotonin-deficient rats are extremely stress-sensitive.

It should be emphasized that the analysis of functional changes in animals lesioned with neurotoxic indoleamines is extremely complicated. Such analysis should ideally include a correlation between the behavioral or neuroendocrine data with a number of biochemical and structural parameters, such as the extent and selectivity of the drug-induced lesion, the drug-induced changes in the activity of the serotonergic neurons, the changes in receptor sensitivity, the extent and location of degeneration, and the time course of the drug-induced effects. It seems particularly important to remember that a reduction in serotonin in the CNS induced by a neurotoxic indoleamine is very different from a reduction induced, say, by synthesis inhibitors or amine-depleting drugs. Thus, for example, a partial reduction in brain 5-HT induced by 5,6- or 5,7-DHT reflects the removal of part of the 5-HT fibers, whereas

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remaining fibers are intact, In fact, such a denervation is probably complete in certain nuclei and partial or absent in others. Moreover, in a brain with a partial destruction of the terminal networks, the functioning of the remaining, intact fibers are likely to change in response to the damage, for example, by an increased or decreased activity.

MODE OF ACTION OF NEUROTOXIC INDOLEAMINES

In order to produce selective neurotoxic effects on central 5-HT neurons, the toxic tryptamines must be provided with a reasonable affinity to the 5-HT uptake sites in brain. The lack of affinity to the 5-HT transport mechanism coincides with a lack of toxicity on serotonin neurons, but, at the same time, with potential toxicity for all nonserotonergic structures in brain. All compounds that have been found to be toxic to monoamine neurons are capable of forming quinone-like metabolites. These metabolites are most likely involved in the molecular mechanism of action of all neurotoxic indoleamines. Based on our present-day understanding of the physicochemical properties of quinones and quinoneimines, the following hypotheses concerning the molecular mechanism of action of the indoleneurotoxins may be formulated: the cytotoxicity may depend on (*a*) formation of hydrogen peroxide, (*b*) covalent irreversible binding of indolequinones to nucleophilic groups of proteins, particularly their SH-groups, and subsequent denaturation of the proteins (48, 49), (*c*) uncoupling of oxidation and phosphorylation and/or arrest of electron transport in respiratory chain enzymes due to replacement of ubiquinones by cytotoxic indolequinones with subsequent block of ATP formation. Irreversible binding of radioactive metabolites of 6-OH-DA, 5,6-, and 5,7-DHT to proteins has been verified in vitro and in vivo, suggesting that protein denaturation may be important for the toxicity of certain indole- and catecholneurotoxins (48–50). The binding of 5,6-DHT, and particularly 5,7-DHT, to monoamine oxidase seems to be an important step in the events leading to toxicity, since monoamine oxidase-resistant α-methylated analogs have reduced in vivo and in vitro effects on NA and 5-HT neurons (6, 21), and since monoamine oxidase inhibitors counteract the toxic effects of 5,7-DHT on NA neurons.

SUMMARY

Taken together, the available data indicate that 5,7-DHT, in combination with ip DMI or monoamine oxidase inhibitors, can be considered a tool for selective lesioning of central 5-HT axons and terminals, useful for the analysis of function of serotonin neurons in various forms of behavior, in neuroendocrine regulation, and in drug interaction. The neurotoxic indoleamines are also important new tools for studies on neuronal ontogeny, regeneration, and plasticity in the CNS.

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Literature Cited

1. Thoenen, H., Tranzer, J. P. 1968. *Arch. Pharmacol. Exp. Pathol.* 261:271–88
2. Uretsky, N. J., Iversen, L. L. 1970. *J. Neurochem.* 17:269–78
3. Ungerstedt, U. 1968. *Eur. J. Pharmacol.* 5:107–10
4. Björklund, A., Baumgarten, H. G., Rensch, A. 1975. *J. Neurochem.* 24: 833–35
5. Gerson, S., Baldessarini, R. J. 1975. *Brain Res.* 85:140–45
6. Baumgarten, H. G., Björklund, A., Nobin, A., Rosengren, E., Schlossberger, H. G. 1975. *Acta Physiol. Scand. Suppl.* 429:1–27
7. Baumgarten, H. G., Björklund, A., Horn, A. S. Schlossberger, H. G. 1974. *Dynamics of Degeneration and Growth in Neurons,* ed. K. Fuxe, L. Olson, and Y. Zotterman, 153–67. Oxford & New York: Pergamon
8. Baumgarten, H. G., Björklund, A., Lachenmayer, L., Nobin, A. 1973. *Acta Physiol. Scand. Suppl.* 391:1–9
9. Björklund, A., Baumgarten, H. G., Nobin, A. 1974. *Adv. Biochem. Psycho. Pharmacol.* 10:13–33
10. Baumgarten, H. G., Evetts, K. D., Holman, R. B., Iversen, L. L., Vogt, M., Wilson, G. 1972. *J. Neurochem.* 19: 1587–97
11. Baumgarten, H. G., Björklund, A., Lachenmayer, L., Nobin, A., Stenevi, U. 1971. *Acta Physiol. Scand. Suppl.* 373:1–15
12. Björklund, A., Lindvall, O. 1975. Unpublished observations
13. Nobin, A., Baumgarten, H. G., Björklund, A., Lachenmayer, L., Stenevi, U. 1973. *Brain Res.* 56:1–24
14. Baumgarten, H. G., Björklund, A., Nobin, A., Rosengren, E. 1975. Unpublished observations
15. Vogt, M. 1974. *J. Physiol. London* 236:483–98
16. Costa, E., Lefevre, H., Meek, J., Revuelta, A., Spano, F., Strada, S., Daly, J. 1972. *Brain Res.* 44:304–8
17. Breese, G. R., Cooper, B. R., Grant, L. D., Smith, R. D. 1974. *Neuropharmacology* 13:177–87
18. Björklund, A., Nobin, A., Stenevi, U. 1973. *Z. Zellforsch.* 145:479–501
19. Lytle, L. D., Jacoby, J. H., Nelson, M. F., Baumgarten, H. G. 1975. *Life Sci.* 15:1203–17
20. Horn, A. S., Baumgarten, H. G., Schlossberger, H. G. 1973. *J. Neurochem.* 21:231–36
21. Björklund, A., Horn, A. S., Baumgarten, H. G., Nobin, A., Schlossberger, H. G. 1975. *Acta Physiol. Scand.* 429: 30–60
22. Iversen, L. L., Uretsky, N. J. 1971. *6-Hydroxydopamine and Catecholamine Nurons,* ed. T. Malmfors and H. Thoenen, 171–86. Amsterdam: North-Holland
23. Gerson, S., Baldessarini, R. J., Wheeler, S. C. 1974. *J. Neuropharmacol.* 13:987–1004
24. Sachs, C. 1971. See Ref. 22, pp. 59–74
25. Björklund, A., Nobin, A., Stenevi, U. 1973. *Brain Res.* 53:117–27
26. Clineschmidt, B. V., Pierce, J. E., Lovenberg, W. 1971. *J. Neurochem.* 18:1593–96
27. Victor, S. J., Baumgarten, H. G., Lovenberg, W. 1974. *J. Neurochem.* 22:541–46
28. Björklund, A., Nobin, A., Stenevi, U. 1973. *Brain Res.* 50:214–20
29. Nobin, A., Baumgarten, H. G., Björklund, A., Lachenmayer, L., Stenevi, U. 1973. *Brain Res.* 56:1–24
30. Baumgarten, H. G., Lachenmayer, L., Björklund, A., Nobin, A., Rosengren, E. *Life Sci.* 12:357–64
31. Baumgarten, H. G., Victor, S. J., Lovenberg, W. 1973. *J. Neurochem.* 21:251–53
32. Baumgarten, H. G., Victor, S. J., Bruckwick, E., Lovenberg, W. 1975. Unpublished observations
33. Baumgarten, H. G., Victor, S. J., Lovenberg, W. 1975. *Psychopharmacol. Commun.* 1:75–88
34. Baumgarten, H. G., Lachenmayer, L., Schlossberger, H. G. 1972. *Z. Zellforsch.* 125:535–69
35. Baumgarten, H. G., Lachenmayer, L. 1972. *Z. Zellforsch.* 135:395–414
36. Baumgarten, H. G., Björklund, A., Lachenmayer, L., Rensch, A., Rosengren, E. 1974. *Cell. Tiss. Res.* 152:271–81
37. Björklund, A., Baumgarten, H. G., Lachenmayer, L., Rosengren, E. 1975. *Cell Tissue Res.* 161:145–55
38. Baumgarten, H. G., Björklund, A., Holstein, A. F., Nobin, A. 1972. *Z. Zellforsch.* 129:256–71
39. Baumgarten, H. G., Göthert, M., Holstein, A. F., Schlossberger, H. G. 1972. *Z. Zellforsch.* 128:115–34
40. Baumgarten, H. G., Groth, H. P., Göthert, M., Manian, A. 1974. *Arch. Pharmacol.* 282:245–54

41. Breese, G. R., Cooper, B. R. 1975. *Brain Res.* 98:517–28
42. Baumgarten, H. G., Björklund, A. 1975. Unpublished observations
43. Longo, V. G., Scotti de Carolis, A., Liuzzi, A., Massotti, M. 1974. *Adv. Biochem. Psychopharmacol.* 10:109–20
44. Koe, B. K., Weissman, A. 1968. *Adv. Pharmacol.* 6B:29–47
45. Müller, E. E., Baumgarten, H. G., Gil-Ad, I., Udeschini, G., Cocchi, D. 1975. Unpublished observations
46. Skyler, J., Baumgarten, H. G., Lovenberg, W. 1975. Unpublished observations
47. Wuttke, W., Baumgarten, H. G., Björklund, A. 1975. Unpublished observations
48. Victor, S. J., Baumgarten, H. G., Bogdanski, D. F., Lovenberg, W. Schlossberger, H. G., 1975. Unpublished observations
49. Baumgarten, H. G., Björklund, A., Bogdanski, D. F. 1975. *Chemical Tools in Catecholamine Research,* ed. G. Jonsson, T. Malmfors, Ch. Sachs, 59–66. Amsterdam: North-Holland
50. Saner, A., Thoenen, H. 1971. *Mol. Pharmacol.* 7:147–54

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