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Effects of Antidepressants and Other Psychotropic Drugs on Melatonin Release and Pineal Gland Function

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With 4 Figures

Summary

Antidepressants and some other psychotropic drugs affect the synthesis and release of melatonin through several mechanisms. Monoamine oxidase (MAO)-inhibiting antidepressants increase pineal concentrations of the melatonin precursors, serotonin (5-HT) and N-acetyl serotonin (NAS), in rodents, and also increase pineal N-acetyl transferase activity as well as both daytime and nighttime plasma melatonin concentrations; they also elevate melatonin, 5-HT and NAS in the cerebrospinal fluid of non-human primates. In humans treated with the MAO-A selective inhibitor, clorgyline, or the nonselective inhibitor, tranylcypromine, increased plasma melatonin also occurs; in contrast, the MAO-B selective inhibitor, l-deprenyl, does not affect plasma melatonin. Chronically-administered tricyclic antidepressants with prominent effects on monoamine uptake and on β-adrenoceptors reduce pineal and plasma melatonin in rodents; however, in two studies in depressed patients, either no change or a significant elevation in nocturnal plasma melatonin followed 3 to 4 weeks treatment with desipramine. As depressed patients in these and several other recent studies had lower pretreatment nighttime melatonin peaks than controls, these findings may be relevant to the presynaptic and receptor adaptational consequences of chronic antidepressant drug treatment. The significant effects on melatonin of other drugs which affect monoamine function and have psychotropic effects, including lithium, propranolol, amphetamine and several monoamine precursors, together with recent observations of the existence of muscarinic and benzodiazepine receptors in the pineal gland are in accord

with previous suggestions that the study of pineal function and melatonin production provides a valuable model system for psychopharmacological investigations.

Key words: Melatonin, serotonin, norepinephrine, monoamine oxidase inhibitors, β-adrenoceptors, monkeys, cerebrospinal fluid, tricyclic antidepressants, lithium, neuroleptics, L-dopa, 5-hydroxytryptophane.

Introduction

Elegant studies over the past two decades have delineated a sequence of regulatory mechanisms controlling the diurnal pattern of melatonin synthesis and release from the pineal gland. These studies have been the subject of several reviews and recent books (*Axelrod,* 1974; *Axelrod, Fraschini* and *Velo,* 1982; *Relkin,* 1983; *Waldhauser* and *Wurtman,* 1983). The influence of an environmental factor, light, on the production of a hormone, melatonin, via an intricate chain of events involving a retinal-hypothalamic pathway, the sympathetic nervous system and metabolic events in the pineal gland has provided a useful model for investigations in several areas of neurobiology.

Drug effects on melatonin synthesis via its dominant regulatory enzyme, N-acetyl transferase (NAT), in rodents and in pineal gland culture systems contributed greatly to early hypotheses about this model system (*Klein* and *Rowe,* 1970; *Deguchi* and *Axelrod,* 1972; *Axelrod,* 1974). Recently, interest has developed in using melatonin production as an index of the effects of antidepressants and other drugs in humans. This approach has been further stimulated by a series of reports of altered melatonin production in depressed patients (*Mendlewicz et al.,* 1979; *Claustrat et al.,* 1984; *Beck-Friis et al.,* in press; *Brown et al.,* 1985 a), and of reports of changes in pineal and plasma melatonin concentrations which follow chronic but not acute treatment with some tricyclic antidepressants in rodents (*Heydorn et al.,* 1982; *Cowen et al.,* 1983 a).

This paper provides a summary and new data from several recent studies by our group investigating the effects of one class of antidepressants, the MAO-inhibitors, on plasma melatonin in humans and on cerebrospinal fluid concentrations of melatonin and its two precursors, serotonin (5-HT) and N-acetyl serotonin (NAS), in rhesus monkeys (*Garrick et al.,* 1985; *Murphy et al.,* in press a). It also provides a review of the effects of the tricyclic and other antidepressants on melatonin production studied in humans and rodents. The changes in melatonin and in pineal gland metabolism produced by these and other psychotropic drugs are discussed in regard to their contributions to current understanding of both the mechanism of action of these drugs and possible implications for modifications in current hypotheses of the regulation of melatonin production and release in humans and other species.

Effects of Monoamine-Oxidase Inhibiting Antidepressants on Melatonin and Pineal Gland Function

An important element in current interpretations of the mechanisms of action and potential clinical significance of the effects of antidepressants and many other psychotropic drugs on physiologic systems is a better understanding of the consequences of the chronic administration of these drugs. Longer-term treatment with low, clinically-relevant doses of psychotropic drugs is now known to elicit adaptational changes in receptors and other synaptic processes which differ from those observed after *in vitro* or after acute, high dose *in vivo* treatment. Nonetheless, both types of studies are important, and usually provide complimentary information.

Early *in vitro* studies of the MAO inhibitors pheniprazine or harmine demonstrated an increase in ^{14}C-melatonin produced from preadministered ^{14}C-5-HT in rat pineal glands maintained in primary organ culture (*Axelrod, Shein* and *Wurtman,* 1969; *Klein* and *Rowe,* 1970). *Snyder, Axelrod* and *Zweig* (1967) had previously reported that pheniprazine prevented the usual nighttime fall in rat pineal gland melatonin content.

Although these original investigations with MAO inhibitors *in vitro* as well as other studies (*Wurtman* and *Ozaki,* 1978) suggested that an increased availability of 5-HT and NAS within pinealocytes might directly lead to increased melatonin release, subsequent studies in intact rats demonstrated that the increased daytime pineal melatonin content and increased NAT activity which followed treatment with either harmine or another MAO-inhibitor, pargyline, was blocked by pretreatment with the β-adrenoceptor antagonist, propranolol (*King, Richardson* and *Reiter,* 1982). This evidence was in keeping with the predominant view developed by *Axelrod* and his coworkers that in the intact animal NAT activity and melatonin synthesis are primarily regulated by noradrenergic input to the pineal gland in response to circadian and seasonal changes in light, acting through the well-delineated retinal-hypothalamic-pineal circuit (*Axelrod,* 1974; *Klein* and *Moore,* 1979). Acute MAO-inhibition thus was interpreted as acting to increase functional norepinephrine in sympathetic neurons and thus enhance stimulation of pineal β-receptors.

In chronic studies with MAO-inhibitors, repeated administration of nialamide for 7 days produced significant reductions in rat pineal and serum melatonin responses to isoproterenol or darkness (*Heydorn et al.*, 1982). These changes were opposite to those produced by a single large dose (40 mg/kg) or nialamide, which led to several-fold increases in daytime melatonin concentrations in both serum and the pineal gland. As the melatonin changes after chronic nialamide administration occurred in conjunction with a decrease in the binding of the β-adrenoceptor ligand, ^{3}H-dihydroalprenolol, to pineal gland homogenates, this change in melatonin release was interpreted as due to the development of β-adrenoceptor subsensitivity during chronic antidepressant treatment.

Increased Daytime and Nighttime Melatonin Release into the Cerebrospinal Fluid of Non-Human Primates During Chronic MAO-Inhibitor Treatment

To begin to evaluate in a primate species the possible influence of chronic MAO inhibition on cerebrospinal fluid melatonin, rhesus monkeys were studied prior to and in the fourth week of treatment with low doses of either clorgyline, a selective inhibitor of MAO type A or l-deprenyl, a selective inhibitor of MAO type B (*Garrick et al.*, 1985; *Murphy et al.*, in press, a).

Prior to the study, the animals were adapted over a several month period to several day periods of chair restraint, which allowed free movement of arms and legs. Automatically controlled lights (500 lux at eye level) were on from 7 a.m. to 7 p.m. and off from 7 p.m. to 7 a.m. To provide continuous CSF sampling, a polyethylene cannula was inserted between the lumbar vertebrate of the animal and advanced to the high cervical subarachnoid space during ketamine anesthesia. CSF collection began at least 24 hours following the lumbar puncture procedure to provide a post-anesthesia recovery time. CSF was withdrawn continuously at a flow rate of approximately 1.5 ml/hour and collected in 90 min aliquots during a baseline period of 1–3 days, with intramuscular saline injections given daily at 3 p.m. Animals were then returned to their individual cages and treated chronically with clorgyline (1 mg/kg/day) or deprenyl (2 mg/kg/day) for 24 days. These doses were chosen on the basis of human, monkey and rodent studies as most likely to yield selective MAO-A or MAO-B inhibition, respectively, during long-term administration (*Garrick et al.*, 1984; *Garrick et al.*, unpublished data). On day 24, the animals were re-anesthetized, lumbar punctures were performed and

cannulae inserted, and the animals were chaired for 1–3 days of CSF collection beginning at least 24 hours after surgery. Daily clorgyline or l-deprenyl administration at the same dose was continued at 3 p.m. each day during this period.

Melatonin was measured in CSF aliquots using a radioimmunoassay (*Rollag* and *Niswender*, 1976) which was previously validated for primate CSF melatonin (*Reppert et al.*, 1979). NAS and 5-HT in CSF were measured by mass spectrometric techniques described elsewhere (*Taylor et al.*, 1985). The CSF levels of melatonin for the light and dark phases of the lighting cycle under both pretreatment and drug treatment conditions were compared using analysis of variance. For those monkeys studied for two or more consecutive nights, the data were combined before statistical analysis to yield mean 90-minute values for each monkey.

As indicated in Fig. 1, mean nighttime CSF melatonin concentrations were three- to four-fold higher than daytime levels during both the baseline study period and during the treatment periods with both MAO-inhibitors ($p < 0.05$ or < 0.01). The clorgyline-treated monkeys demonstrated a five-fold increase in mean CSF melatonin concentrations during the day ($p < 0.01$) and a 3.5 fold increase at night ($p < 0.001$). In contrast, deprenyl administration did not significantly alter CSF melatonin concentrations during the day or night. The time of the nighttime peak melatonin concentration, which occurred between 11.45 a.m. and 12.15 p.m., was not significantly affected by either drug treatment. In preliminary studies in two monkeys, the increased CSF melatonin concentrations which followed clorgyline treatment during both the day and night were found to be associated with increased CSF 5-HT and NAS concentrations as well (Fig. 2 a and 2 b).

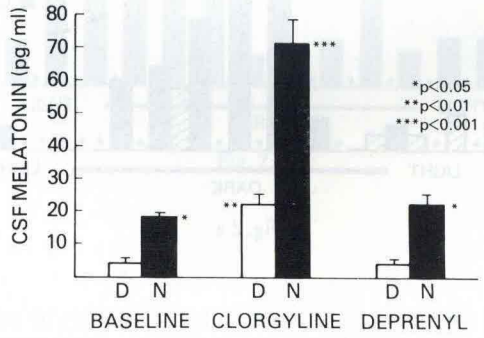

Fig. 1. CSF melatonin changes after clorgyline and deprenyl in rhesus monkeys

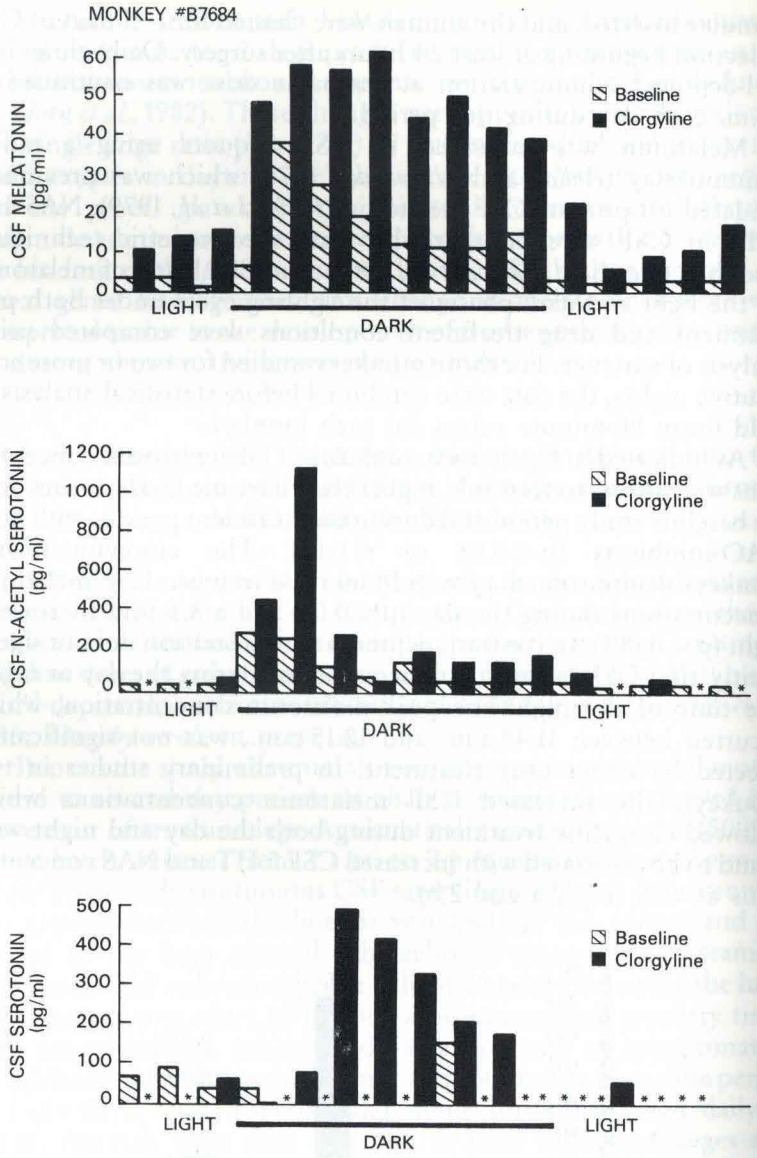

Fig. 2 a

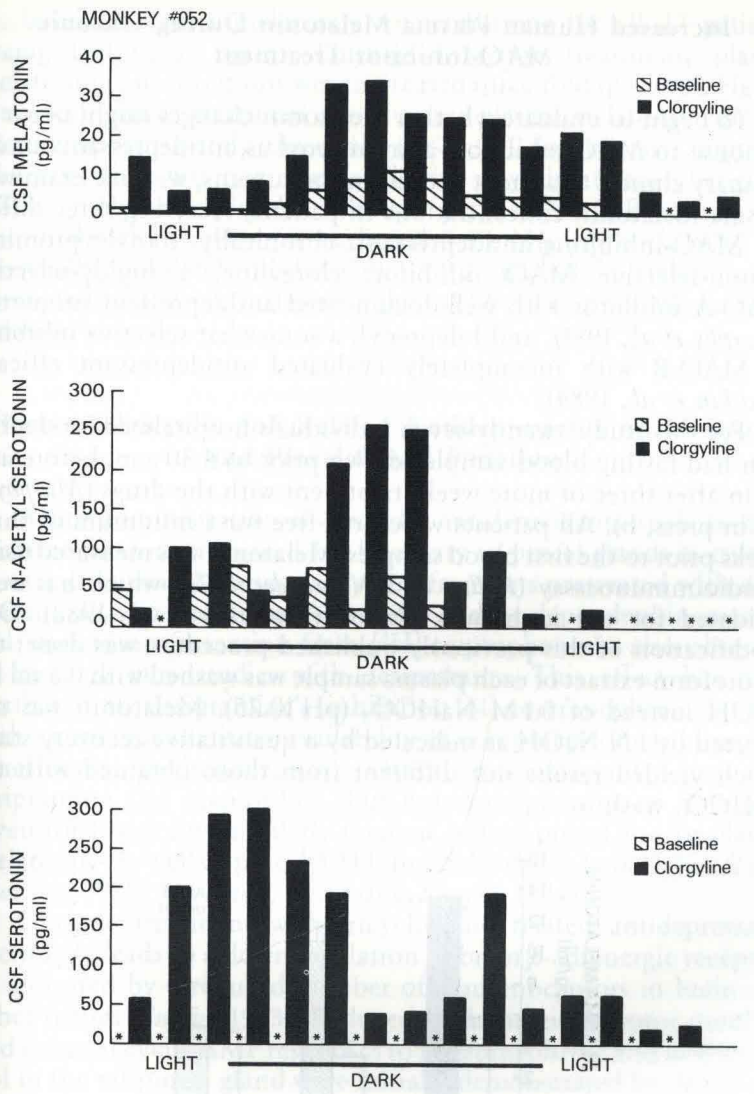

Fig. 2 b

Figs. 2 a, b. Effects of chronic clorgyline administration on *CSF melatonin, N-acetyl serotonin* and *serotonin* concentration over a 12 h/12 h light/dark cycle in two individual monkeys

Increased Human Plasma Melatonin During Chronic MAO-Inhibitor Treatment

To begin to evaluate whether melatonin changes might occur in response to MAO-inhibitors administered as antidepressants under ordinary clinical treatment conditions in humans, we have examined plasma melatonin concentrations in patients receiving three different MAO-inhibiting antidepressants chronically: tranylcypromine, a non-selective MAO inhibitor; clorgyline, a highly-selective MAO-A inhibitor with well-documented antidepressant properties (*Murphy et al.*, 1981), and l-deprenyl, a somewhat selective inhibitor of MAO-B with incompletely evaluated antidepressant efficacy (*Quitkin et al.*, 1984).

For this study, twenty-seven individuals hospitalized for depression had fasting blood samples drawn prior to 8.30 a.m. before and again after three or more weeks treatment with the drugs (*Murphy et al.*, in press, b). All patients were drug-free for a minimum of three weeks prior to the first blood samples. Melatonin was measured using a radioimmunoassay (*Rollag* and *Niswender*, 1976) which has been validated for use in human plasma (*Tamarkin et al.*, 1982). One modification of this previously published procedure was done: the chloroform extract of each plasma sample was washed with 0.5 ml 1 N NaOH instead of 0.1 M $NaHCO_3$ (pH 10.25). Melatonin was not affected by 1 N NaOH as indicated by a quantitative recovery study which yielded results not different from those obtained with the $NaHCO_3$ wash.

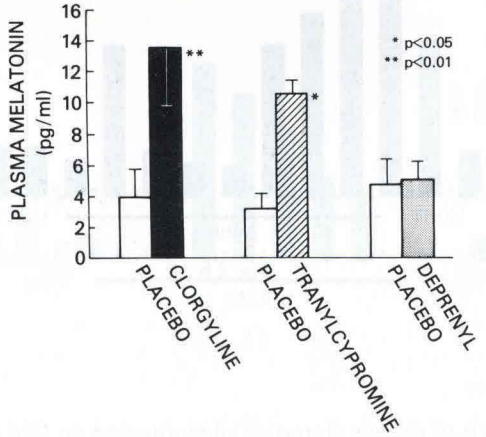

Fig. 3. Plasma melatonin changes following chronic monoamine oxidase inhibitor administration to depressed patients

Baseline plasma melatonin concentrations for all 27 patients averaged 4.0 ± 0.9 pg/ml. During clorgyline treatment, plasma melatonin concentrations were increased three-fold ($p < 0.01$, Fig. 3). Tranylcypromine treatment also elevated plasma melatonin concentrations approximately three-fold ($p < 0.05$). In contrast, deprenyl administration was not associated with any significant change in plasma melatonin (Fig. 4), although platelet MAO-B activity determined with benzylamine as the substrate (*Murphy et al.*, 1976) was essentially completely inhibited (0.3 ± 0.2 nmols/10^8 platelets/hour), compared to the pretreatment values (13.9 ± 1.6, $p < 0.01$) in these patients.

Effects of Tricyclic and Related Antidepressants on Melatonin and Pineal Gland Function

Acute administration of tricyclic antidepressants such as desipramine produce increased NAT activity in pineal glands in culture as well as in pineal glands extirpated from rats pretreated with desipramine (*Parfitt* and *Klein*, 1976, 1977). A dose-dependent increase in [^{3}H]-melatonin formation from [^{3}H]-tryptophan was also observed in these *in vitro* studies with desipramine. This effect has been attributed to desipramine's inhibition of norepinephrine uptake, with a consequent greater availability of norepinephrine to stimulate pinealocyte β-adrenoceptors. Other antidepressants including imipramine and maprotiline (but not clomipramine or iprindole) given for 1 to 3 days similarly increase rodent pineal and/or plasma melatonin—as well as pineal 5-HT and NAS (*Wirz-Justice, Arendt* and *Marston*, 1980; *Friedman, Yocca* and *Cooper*, 1984).

Chronic treatment with tricyclic and related antidepressants eventually leads to a down regulation of brain β-adrenergic receptors as indicated by a reduced number of β-adrenoceptors in brain and other tissues (*Sugrue*, 1983). Reduced β-adrenergic receptor numbers and reduced cyclic AMP responses to norepinephrine and isoproterenol in the rat pineal gland were initially demonstrated by *Moyer* and coworkers (1981) to follow treatment with desipramine given chronically but not acutely. In a subsequent study from the same laboratory, repeated desipramine administration to rats significantly reduced the elevations in pineal melatonin content produced by either isoproterenol or darkness, and also significantly blunted the normal nocturnal rise in serum melatonin in the same animals (*Haydorn et al.*, 1982). Partial replication of these results was obtained by *Cowen* and coworkers (1983 a), who reported that treatment for ten

days with desipramine and another tricyclic, amitriptyline, reduced pineal melatonin responses to isoproterenol administration. Nighttime melatonin increases remained unchanged, however, and other antidepressants given chronically, including fluoxetine, mianserin and iprindole did not block isoproterenol's stimulatory action on melatonin release.

Somewhat similar findings also were reported by *Friedman, Yocca* and *Cooper* (1984), who demonstrated that pineal melatonin and NAS as well as NAT activity were all reduced at night during chronic (3–4 weeks) but not acute (3 days) treatment with imipramine or iprindole. Differences in doses and duration of treatment with these antidepressants may have contributed to some of the discrepancies between the results of these studies. For example, *Friedman* and coworkers (1984) found that iprindole-related melatonin changes appeared only after 4 weeks, and not 3 weeks, treatment with the drug.

Only preliminary data on plasma melatonin changes during tricyclic antidepressant drug treatment in man have been reported. Nighttime plasma melatonin concentrations were found to be elevated in six depressed patients studied after treatment with desipramine (2 mg/kg/day) for one week; upon repeated study in the third week of desipramine treatment, melatonin levels remained elevated (*Thompson et al.*, in press). *Brown* and coworkers (1985 b) reported no changes in plasma melatonin after 4 weeks treatment of depressed patients with desipramine. These data were interpreted as arguing against the functional importance of pineal beta-adrenergic receptor down-regulation of melatonin production and release in humans. These data thus stand in contrast with the overall conclusions of the rodent studies summarized above. Similar evidence of an enchancement rather than reduction of adrenergic influence upon pineal N-acetyl transferase activity during tricyclic antidepressant treatment has come from recently reported preliminary data from five depressed patients, which revealed a significantly increased excretion of 6-hydroxymelatonin, the major urinary metabolite of melatonin, during chronic treatment with desipramine (*Golden et al.*, 1985).

Effects of Lithium on Melatonin and Pineal Gland Function

Lithium is a drug of great interest in regard to possible influences on the diurnal and seasonal functions of the pineal gland since lithium has its most prominent therapeutic effects on cyclic, bipolar affective disorders. Its anti-manic effects are well known, and it has

preventative actions on recurrent manic-depressive cycles in bipolar patients as well as recurrent depressive episodes in unipolar depression.

Initially, lithium was shown to inhibit isoproterenol-induced stimulation of cyclic AMP production *in vitro* in pineal homogenates (*Zatz*, 1979). Similar reductions in the effects of isoproteronol on pineal cyclic AMP were observed in rats treated for five weeks with lithium, a change interpreted as reflecting a down-regulation of pineal β-adrenoceptors (*Yocca et al.*, 1983). In addition, lithium administration to rats was associated with reduced nocturnal peaks of pineal melatonin, NAS and NAT activity compared to rats given normal diets or equivalent amounts of sodium chloride. Pineal concentrations of the serotonin precursors and the serotonin metabolite, 5-HIAA, were unchanged, while a 15% reduction in pineal serotonin represented a non-significant difference. Lithium also produced a 1–3 hour time delay in peak pineal NAT activity, although there were no changes in the timing of the NAS or melatonin peaks (*Yocca et al.*, 1983). In another study in which lithium chloride was given for 6 weeks and compared with normal or sodium chloride-treated rats, no change in the magnitude of the nocturnal peaks of serum melatonin was found (*Seggie et al.*, 1983). However, in this study, serum melatonin peaks occurred four hours earlier than those of the control groups—a statistically significant difference. In contrast, a number of other investigators have suggested that chronic lithium treatment may delay some neuroendocrine events and physiological responses; the current state of this controversy is discussed by *Seggie* and coworkers (1983). Reconciliation of these discrepant changes in serum melatonin versus pineal melatonin and in other pineal gland functions apparently requires further study. It is of note that chronically-administered lithium, like the tricylic and MAO-inhibiting antidepressants, tends to produce pineal β-receptor down regulation, an effect common to many drugs used in the therapy of the affective disorders.

Effects of Neuroleptics and Related Drugs on Melatonin

Haloperidol increases rat pineal melatonin concentrations approximately 2-fold when given in a single subcutaneous dose of 1 μg/kg one hour before sacrifice (*Gaffori, Geffard* and *Van Ree*, 1983). When [^{3}H]-melatonin is given intravenously, pretreatment with chlorpromazine (20 mg/kg) and other neuroleptics leads to higher blood and brain concentrations of [^{3}H]-melatonin compared to

controls, an effect related to inhibition of melatonin metabolism via 6-hydroxymethylation in the liver; conversely, stimulation of liver drug-metabolizing enzymes by phenobarbital pretreatment leads to lower brain [^{3}H]-melatonin concentrations (*Wurtman, Axelrod* and *Anton-Tay,* 1968). In studies in humans, 15 schizophrenic patients receiving an average dose of 585 mg of chlorpromizine for at least three weeks had CSF melatonin concentrations no different from those of 13 untreated patients or 16 controls (*Beckmann, Wetterberg* and *Gattaz,* 1984). In another study, CSF melatonin was also found to be unaltered by chlorpromazine (100–800 mg/day); however daytime serum melatonin levels were 3 to 5 times higher than those of untreated patients or controls, and were highest in those receiving larger chlorpromazine doses (*Smith, Barnes,* and *Mee,* 1979). As only 5–8 individuals were included in each group and no statistics were presented, this report requires replication.

Effects of Monoamine Precursors, Amine Releasing Agents and Other Drugs on Melatonin and Pineal Gland Function

The catecholamine precursor, L-dopa, increases rat pineal melatonin content when given subcutaneously in single large doses (300 mg/kg) (*Deguchi* and *Axelrod,* 1972; *Lynch, Wang* and *Wurtman,* 1973). Sympathetic denervation following intravenous 6-hydroxydopamine enhances this response. Increased intravascular dopamine formation was originally suggested to mediate this response, but post-synaptic β-adrenoceptor supersensitivity to catecholamines would now seem to be a more likely explanation. The psychomotor stimulant, d-amphetamine, given acutely, increases NAT activity *in vitro* and *in vivo* in rodents, presumably by releasing presynaptic catecholamines, as its *in vivo* effects are nullified by ganglionectomy (*Backstrom* and *Wetterberg,* 1973; *Altar, Terry* and *Lytle,* 1984). In three studies in humans, smaller oral doses of L-dopa produced no melatonin changes (*Arendt,* 1978; *Wetterberg,* 1978; *Vaughn et al.,* 1979).

The serotonin precursor, 5-hydroxytryptophan (5-HTP), given during the day also produces small increases in rat pineal gland melatonin content (*Wurzberger et al.,* 1976). In sheep, 5-HTP given intraperitoneally in doses of 20 to 200 mg/kg produces a 7 to 20-fold increase in daytime concentrations of serum melatonin (*Namboodiri et al.,* 1983). The same 5-HTP doses had no significant effect at night, when melatonin levels were already elevated approximately 15-fold. L-tryptophan given in even larger doses (500 mg/kg) had negligible effects either during the day or at night in this study. The difference between the melatonin changes produced by 5-HTP and by tryptophan were explicated in an investigation of the changes in pineal gland 5-HT and NAS produced by these two indoleamine precursors (*Sugden et al.,* 1985). While intraperitoneal tryptophan increased pineal tryptophan content, it failed to change pineal 5-HT or NAS. In contrast, 5-HTP treatment increased pineal NAS, 5-HT, 5-hydroxytryptophol, 5-hydroxyindoleacetic acid and, as noted above, melatonin. NAT activity remained unchanged after 5-HTP, indicating that the changes in melatonin release were not due to a neurally-mediated increase in the activity of this enzyme as occurs nocturnally.

β-Adrenoceptor blocking drugs such as propranolol or altenolol block nocturnal increases in pineal, blood, CSF and/or urine melatonin in rodents (*Deguchi* and *Axelrod,* 1972), non-human primates (*Reppert et al.,* 1979; *Garrick et al.,* 1983) and humans (*Hanssen et al.,* 1980; *Cowen et al.,* 1983 b). These drugs antagonize some of the peripheral and possible central components of anxiety, and have also been suggested to have some antimanic and antipsychotic properties in large doses, but there is no evidence to attribute their behavioral properties to pineal response differences.

While pharmacologic studies have not yet been accomplished, it is worth noting several new developments with possible implications for regulatory influences by psychotropic drugs on pineal gland function. Muscarinic receptors have been found in sheep and rat pineals; however, as these receptors are not altered by ganglionectomy, they do not appear to be primarily localized on sympathetic nerve terminals (*Taylor et al.,* 1980). In addition, a high density of benzodiazepine binding sites has recently been indentified in rat pinealocytes; benzodiazepine agonists such as diazepam appear capable of prolonging and increasing the magnitude of norepinephrine-induced increases in NAT activity, although relatively high doses (10–50 μM) are required (*Quirion,* 1984; *Matthew et al.,* 1984).

Discussion

The ultimate functional consequences in humans of the combined cellular effects of antidepressants and other psychotropic drug treatments on monoamine uptake, release, metabolism, and receptor sensitivity in the noradrenergic system and the pineal gland remain incompletely understood. It remains possible, for instance, that β-receptor and other neurotransmitter receptor adaptational phenomena suggested to be involved in the effects of chronically-

administered antidepressants on melatonin release are only one element contributing to the mechanism of action of these drugs. Such receptor changes may be important, but also appear to be necessarily integrated with other synaptic alterations (*Murphy et al.*, 1984).

An alternative hypothesis to the receptor adaptation models to explain the recent findings from our group and others studying

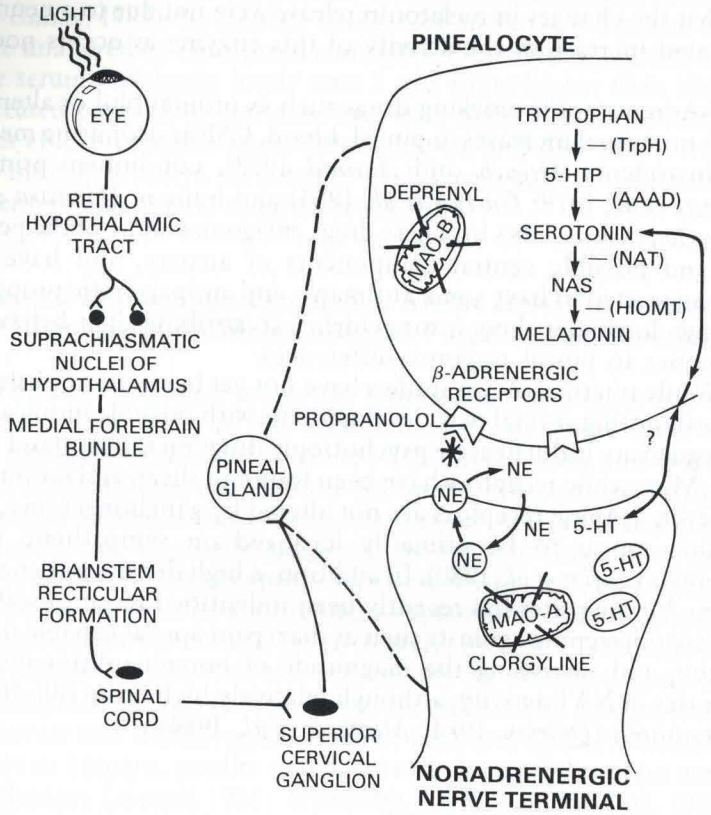

Fig. 4. Diagram illustration of the different sites of action suggested for *clorgyline* and *deprenyl* on *MAO-A* and *MAO-B* and on the availability of *serotonin* and *norepinephrine* in *noradrenergic nerve terminals* and pinealocytes of the pineal gland. The ability of *MAO-A* inhibition (produced by *clorgyline*) but not *MAO-B* inhibition (produced by *deprenyl*) to increase melatonin release suggests that increased *serotonin* and/or *norepinephrine* in the *noradrenergic nerve terminals* is primarily responsible for the melatonin change. Since a variety of other evidence suggests that *clorgyline* treatment ist associated with decreased sympathetic outflow (*Murphy et al.*, b), the more likely hypothesis is that increased serotonin in the *noradrenergic nerve terminal* which can be released into the pinealocyte (*cf. Bertler, Falck,* and *Owman,* 1964) is responsible

MAO-inhibiting antidepressants and large, pharmacologic doses of 5-HTP is based not on possible noradrenergic changes and their effects on pineal function but rather on the recurrent suggestions that increased availability of the melatonin precursor, serotonin, in the pineal gland itself or possibly in the sympathetic neurons innervating the gland (cf., *Bertler et al.*, 1964) can contribute to an increased synthesis and release of melatonin (*Wurtman* and *Ozaki,* 1978; *Waldhauser* and *Wurtman,* 1983) (see Fig. 4).

Snyder and *Axelrod* (1965) first observed that increased daytime pineal gland serotonin levels followed treatment of rats with the non-selective MAO-inhibitor, pheniprazine. Many studies in intact animals and in pineal glands in culture demonstrated enhanced serotonin synthesis and increased concentrations of pineal serotonin following MAO-inhibitor treatment (*Snyder et al.*, 1967; *Klein* and *Rowe,* 1970; *Wurzburger et al.*, 1976). In some of the same patients included in our study of the effects of MAO inhibitors on plasma melatonin, we have found clorgyline and tranylcypromine treatment to be associated with significant, 2-to-3-fold increases in platelet serotonin content (*Murphy et al.*, unpublished data). While, as noted above, serotonin availability has occasionally been mentioned as a possible factor regulating melatonin production, it would now seem that the large changes in pineal serotonin stores which follow MAO-A inhibition may be associated with enhanced melatonin output, as exemplified in our results in humans and in our similar studies showing markedly enhanced daytime and nighttime CSF 5-HT, NAS and melatonin concentrations following chronic treatment with clorgyline in monkeys. In support of this hypothesis, some but not all studies observed increased daytime plasma melatonin after administration of the serotonin precursors, 5-hydroxytryptophan and L-tryptophan, and the MAO-inhibitors, pargyline and nialamide, in rodents and in sheep (*Wurzberger et al.*, 1976; *Heydorn et al.*, 1982; *Namboodiri et al.*, 1983; *Sugden et al.*, 1985). Further elucidation seems required of the pineal melatonin synthesis mechanisms and in particular the nature of the interactions between noradrenergic input into the pinealocytes and the apparent semi-autonomous capacity of the pinealocyte to synthesize melatonin under at least some conditions such as those which follow pharmacologic interventions (*e.g.* treatment with MAO-inhibitors or serotonin precursors).

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