Biochemical Pharmacology, Vol. 31, No. 23, pp. 3717–3721, 1982.
Printed in Great Britain.

0006-2952/82/233717-05 $03.00/0
Pergamon Press Ltd.

COMMENTARY

THE INTERACTION BETWEEN LEAD AND CATECHOLAMINERGIC FUNCTION

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Over the past decade, the suggestion that childhood hyperactivity is related to exposure to lead [1] has received much attention. Initially proposed on epidemiological grounds, this suggested relationship has been further examined in numerous animal studies (e.g. Ref. 2) designed as models of the clinical condition. However, the findings of these have been inconsistent, and a clear picture of the relationship between exposure to lead and behavioural dysfunction has been slow to emerge.

It was suggested that lead might cause an alteration in brain catecholamines because of the known correlation between hyperactivity and catecholaminergic function [3]. In laboratory animals hyperactivity can be produced by pharmacological or physical modification of brain catecholamine levels, and it has been proposed that the basis of lead-induced hyperactivity might be some alteration of catecholaminergic function. Since the first report of the possible involvement of brain catecholamines in lead-induced hyperactivity [4], this aspect of the neurotoxicity of lead has received much attention.

Neurochemical experiments

In vitro *studies*. Several aspects of the effect of lead on catecholaminergic neurochemistry, including metabolism of precursors and cofactors, synthesis, release, uptake and postsynaptic receptor activity have been studied *in vitro*.

Purdy *et al.* [5] reported that lead concentrations as low as 10^{-8} M produced a 35% inhibition in the synthesis of biopterin, decreasing to 55% inhibition at 10^{-5} M. Biopterin (5,6,7,8-tetrahydrobiopterin) is a cofactor for both the hydroxylation of phenylalanine to tyrosine, and for the hydroxlation of tyrosine to the catecholamine intermediate L-3,4-dihydroxyphenylalanine (L-DOPA). These authors also reported that the salvage pathway which regenerated oxidized biopterin was affected at lead concentrations above 10^{-6} M, due to irreversible inhibition of dihydropterin reductase.

A preliminary study of the synaptosomal conversion of tyrosine to dopamine suggested enhancement of catecholamine synthesis in the presence of lead at concentrations of 10^{-7}–10^{-4} M [6]. However, the activity of tyrosine hydroxylase, the initial and rate limiting enzyme step in the catecholamine synthetic pathway, appeared unaffected by lead at concentrations of 10^{-3} M in both the striatum and hypothalamus [7].

Inorganic lead has also been shown to block uptake and release of dopamine by synaptosomes. Concentrations of 5×10^{-5} M [8], 10^{-4} M [9] and 10^{-5} M [10] significantly inhibited uptake. The effect of lead on the synaptosomal release of dopamine appears less certain. According to one report only calcium-dependent release at a level of 10^{-4} M [8] was increased; two other studies of resting release of dopamine gave conflicting results, a concentration of inorganic lead of 10^{-5} M stimulating release in one [9] and up to 10^{-4} M producing no change in another [10].

Lead has been shown to block postsynaptic adenylate cyclase activity at concentrations below 3×10^{-6} M [11]. This enzyme may be coupled to dopamine receptors and alterations in its function may produce changes in dopaminergic activity.

These *in vitro* findings are hard to relate to lead effects on the intact nervous system. The most important question to be considered is the physiological significance of the concentration of lead present in the experimental system. Neonates from maternal rats consuming 4% $PbCO_3$ in their diet (32,000 ppm Pb) and subsequently weaned to 40 ppm Pb have total brain lead concentrations in the range 2.9×10^{-6}–4.3×10^{-6} M (wet weight; data from Ref. 4). While it is important to recognize that the brain is not homogeneous and that localized increases in concentrations of lead will exist in certain areas [12] or intracellular compartments [13], any *in vitro* studies reporting changes at concentrations above these values seem unlikely to have much relevance to *in vivo* exposure.

In vivo *experiments*. Early research concentrated on the effects of lead on endogenous levels of neurotransmitters. There were reports of increases of noradrenaline in the whole brain [14], forebrain [15], midbrain [16] or brainstem [17]; however other workers reported no changes (e.g. Refs. 4, 18 and 19).

For dopamine, some workers found no changes in lead-exposed animals [14, 15, 18, 19] while others reported decreases in dopamine levels in the whole brain [4], striatum [17] and the cortex, midbrain and hypothalamus but not the striatum [16]. Many of these studies did not report lead levels. However, Schumann [20] showed that rats with blood leads up to 486 μg/100 ml and brain leads up to 7.5 ppm had no significant alterations in endogenous levels of tyrosine, dopamine or noradrenaline.

Data also exist for *in vivo* uptake and release of catecholamines. Silbergeld and Goldberg [15] reported a decrease in high-affinity dopamine transport and an increase in high-affinity transport in mice drinking water containing 5 g of Pb/l. (as the acetate) (2731 ppm Pb). However, a later study by Wince *et al.* [21] on the offspring of rats fed with 4% lead carbonate weaned to 40 ppm Pb showed no changes in the differences in dopamine uptake or tyrosine utilization. As this study used pair-fed animals to control for the effects of undernutrition, it is possible that the earlier findings were complicated by indirect effects of lead (e.g. via nutritional deficiencies).

It was also apparent that whole-brain assessment and simple estimation of monoamine concentrations are poor measures of change (for a review see Ref. 22). Finally, the problem of reproducibility of results was elegantly summarized in Golter and Michaelson [14], who described difficulties in reproducing their earlier results. As a result later studies have concentrated on more specific aspects of catecholaminergic function.

Catecholamine turnover rates were reported to be unchanged except in one study where whole-brain noradrenaline turnover was found to be increased [14]. It should be noted that turnover studies utilize the inhibition of an enzyme of transmitter synthesis (usually tyrosine hydroxylase) and the measurement of the accumulation of catecholaminergic intermediates. If lead were to cause an alteration at the level of the synthesizing enzymes then these methods would be unlikely to detect any lead effect.

Other markers of catecholaminergic turnover are the measurements of the metabolites of dopamine (homovanillic acid—HVA) and noradrenaline (vanillymandelic acid—VMA). Silbergeld and Chisholm [23] reported that HVA was increased by 33% in brain and 265% in urine, and VMA was increased by 48% in brain and 216% in urine in mice given 5 g of Pb. (2731 ppm Pb) from birth. It is likely that increased urinary metabolite levels reflect peripheral catecholamine breakdown; therefore this dose of lead appears to affect both peripheral and central metabolisms. This study also reported that the urinary concentrations of these metabolites, especially HVA, were elevated in lead-exposed children (i.e. children with blood lead in the range 59–68 μg/100 ml).

In a study of dopaminergic turnover in rats dosed with 2.5 g of Pb/l. (as the acetate) (1365 ppm Pb), Govoni *et al.* [24] reported that dihydroxyphenylacetic acid (DOPAC, a reliable indirect index of functional ability of dopaminergic neurones) and HVA concentrations were significantly decreased in the striatum. These authors also noted that serum prolactin levels (hypothalamic secretion of dopamine inhibits prolactin release) were virtually doubled in these animals.

In a later study using a similar dosing regime Govoni *et al.* [25] reported that besides being decreased in the striatum, DOPAC activity was unchanged in the substantia nigra and increased in the nucleus accumbens and frontal cortex. The animals in both studies were reported to have increased locomotor activity. It should be noted that in the earlier study lead-dosed animals were 10–15% lighter. The reported increase of DOPAC in the nucleus accumbens was concluded to be due to an enhancement of dopamine synthesis, which could be correlated with the increase in motor activity. The other changes were more difficult to interpret, and Memo *et al.* [26] suggested that interactions with other neurotransmitter systems might account for them. These authors confirmed previous findings and reported the variable DOPAC changes in different CNS regions to be both dose-dependent [at 0.04 g of Pb/l. (218 ppm Pb) and 2.5 g of Pb/l. (as the acetate) (1365 ppm Pb)] and reversible (these changes had returned to normal 30 days after cessation of treatment).

Further reinforcement of these findings came from Lucchi *et al.* [27] who reported reciprocal receptor changes in striatum (increased) and nucleus accumbens (decreased) by measuring (−)[^{3}H]sulpiride stereospecific binding (a substituted benzamide believed to be a specific ligand for dopamine D_2-receptors) in rats dosed throughout life with 2.5 g of Pb/l. (as the acetate) (1365 ppm Pb). These authors concluded that the earlier reports of DOPAC changes were consistent with their results, i.e. an increase in dopamine synthesis caused a decrease in receptor sensitivity and vice versa. It is pertinent to note that these authors found no differences in spiperone-specific binding (a label for both D_1- and D_2-receptors but with preferential labelling of D_2) in the areas studied. There is also the added complication that sodium increases the potency of sulpiride up to 50-fold, so that butaclamol displaceable [^{3}H]domperidone provides a more appropriate antagonist system for labelling D_2-receptors.

Finally, as the receptor-linked adenyl cyclase (dopamine D_1) in forebrain synaptosomes [21, 28], the receptor-linked guanyl cyclase activity [29], and the noradrenaline-sensitive adenyl cyclase in the cerebellum [30] have been reported to be changed, the possible receptor alterations induced by lead remain inconclusive.

Recently, the interaction between lead and tetrahydrobiopterin metabolism has received attention. *In vivo* as well as *in vitro* and serum biopterin derivative levels have been positively correlated ($P < 0.001$) with blood lead levels in human patients [31]. Male rats receiving 5 mg of Pb/l. in their drinking water (5 ppm Pb) since weaning also show a significant ($P < 0.02$) positive correlation between blood lead and plasma dihydrobiopterin after 3 months but show a fall in plasma dihydrobiopterin after 7 months [32].

Biopterin metabolism appears to be one of the most sensitive biochemical systems to lead, comparable to *d*-amino laevulinic acid synthesis, but the details of this system have not been fully investigated particularly with respect to adaption.

Pharmacological challenge experiments

Drug challenge is a useful method for exploring the functional consequences of relatively subtle alterations in CNS mechanisms. The administration of centrally acting agonists or antagonists to lead-dosed animals has been carried out in an attempt to uncover changes which may be obscured by the

diverse neurochemical balances underlying normal behaviour.

Amongst catecholaminergic agonists, the most frequently used drug has been amphetamine, which usually produces an increase in locomotor activity. Silbergeld and Goldberg [33] reported a paradoxical decrease in activity induced by *l*- and *d*-amphetamine in mice given drinking water loaded with 10 g of Pb/l. (as the acetate) (5462 ppm) and showing undernutrition and hyperactivity. Sobotka and Cook [34] reported that amphetamine-induced locomotor activity was attenuated in rats given 81 mg of Pb/kg orally from post-natal day 3 to day 21 and suffering from undernutrition but not hyperactivity. A diminished responsiveness to amphetamine was also reported by Reiter *et al.* [35] in a long-term study (from 40 days preconception in mothers and throughout life in their offspring) in rats exposed to 5 and 50 ppm Pb and showing no weight gain differences and reduced activity. Memo *et al.* [36] reported that rats given 2.5 g of Pb/l. (as the acetate) (1365 ppm Pb) exhibited hyperactivity, and showed a decrease in amphetamine-induced activity.

In each of these studies amphetamine-induced locomotor activity in lead-dosed animals has been reported to be either: (i) attenuated (seen as a diminished responsiveness to the drug), or (ii) paradoxically decreased. Interestingly, this alteration is independent of any initial activity state.

Other dopamine agonists have been used. In a neuropharmacological study in mice Silbergeld and Goldberg [15] reported a number of catecholaminergic changes in mice dosed with 5 g of Pb/l. (as the acetate) (2731 ppm Pb), and showing undernutrition and hyperactivity. Enhancement of catecholaminergic function was achieved with L-DOPA, benztropine (which inhibits catecholamine uptake) and apomorphine (a direct receptor agonist). These drugs all caused an exacerbation of existing hyperactivity in lead-dosed animals with minimal or no effects in controls. The paradoxical decrease of amphetamine-induced activity was reproduced with both amphetamine and methylphenidate (a structurally related drug). This was also seen with fenfluramine (a phenylethylamine known to affect animergic pathways). The tyrosine hydroxylase inhibitor alphamethylparatyrosine greatly reduced motor activity in lead-dosed animals while controls were not significantly affected. This treatment also appeared to reverse the effect of amphetamine, so that lead-treated animals responded like naive controls.

Antagonists of catecholaminergic function have also been used. The neuroleptics haloperidol (a centrally acting butyrophenone) and (−)sulpiride have been administered to lead-dosed animals. Lucchi *et al.* (27) found that rats dosed with 2.5 g of Pb/l. (as the acetate) (1365 ppm Pb) showed no differences in haloperidol-induced sedation, while the dose of (−)sulpiride which caused sedation was lower in lead-intoxicated animals than in control rats. These observations suggest that one of the neurochemical changes that may be ascribed to lead is an alteration in receptors sensitive to (−)sulpiride, i.e. a discrete population of dopaminergic (D_2) receptors.

In each of these studies, catecholaminergic function has been shown to be altered in some manner. However, the reported somatic or nutritional changes make assessment of these results difficult. Michaelson [37] has evaluated the effects of various levels of undernutrition on later levels of locomotor activity and response to amphetamine. A statistically significant relationship was found between body weight and change in activity both before and after injection. It is evident that undernutrition, and not lead per se may be at least partially responsible for some of the behavioural effects previously reported. Carmichael *et al.* [38] have shown that the effects of undernutrition (an observable index of indirect toxicity) becomes evident at dose levels of about 1000 ppm Pb in drinking water, so that findings of studies employing doses above this level must be interpreted with caution.

The problems of overt toxicity and subtoxic lead exposures have been addressed in other studies. Wince *et al.* [21] used the offspring from maternal rats who had received 4% $PbCO_3$ in the diet and weaned to 40 ppm Pb, but with pair-fed animals to control for the effects of undernutrition. Lead-dosed animals were significantly more active than controls, but there were no statistical differences in amphetamine- and apomorphine-induced motility between groups. These results suggest that the previously observed effects of catecholaminergic agonists using high levels of lead exposure were possibly due to indirect lead-induced changes.

In a low-dose study rats receiving 25 and 75 mg/kg lead acetate by mouth from post-natal 2 to day 14 had blood leads at day 15 of 50 and 100 μg Pb/100 ml respectively [39]. There were no somatic differences between lead-dosed and control animals up to 35 days, when the experiment was terminated. At this age there were no significant differences in activity between groups. Activity scores fell after a predrug injection of saline, possibly due to habituation of animals to the apparatus. The low-dose groups had significantly lower activity than control or high-dose groups. This phenomenon was also evident and statistically significant after amphetamine injection at a dose of 1 mg/kg. This effect of lead was not significant at a high dose of amphetamine (5.0 mg/kg) although qualitative assessment of activity showed that low-dose animals exhibited more stereotyped behaviour than the other two groups. These results are difficult to interpret, but suggest that lead exposure at low doses might be causing a direct alteration in amphetamine-mediated mechanisms.

Support for this idea comes from Rafales *et al.* [40]. Their study reported no change in activity in rats dosed with 109 ppm Pb postnatally. The possibility of observable general toxicity at this dose is extremely unlikely and blood lead levels were reported in the 'normal' human range (20–30 μg Pb/100 ml). However, amphetamine administration to male rats caused a significant (21%) increase in locomotor activity over that of controls. The observation that agonist challenge causes an increase in activity (not a decrease) at very low levels of lead is further supported by results from our laboratory, where rats dosed perinatally with 300 and 1000 ppm

Pb also show an altered catecholaminergic function. Rats exposed through gestation and lactation to 300 and 1000 ppm Pb and weaned onto tap water have been shown to have blood leads at weaning of 40 and 85 μg Pb/100 ml respectively [38]. Adult male rats exposed to this regime showed no significant differences in open-field activity from controls. However, an increased responsiveness to stimulation of locomotor activity by apomorphine and only marginal changes with amphetamine were found in lead-treated animals, and higher scores were found in the lower-dose group [41].

As there may be nonspecific somatic effects in the high-dose group, the absence of a dose–response relationship suggests that lead may stimulate catecholaminergic function before it becomes impaired by the more general manifestations of toxicity. The disparity between amphetamine- and apomorphine-induced locomotor behaviour points to stimulation mediated through a receptor change.

To summarize, research has become increasingly orientated to doses of lead relevant to human exposure. The measurement of blood lead makes correlation between studies easier, and is a useful index of exposure, helping to clarify the bewildering number of regimens of lead administration that have been reported. There may be more accurate ways of assessing lead load, but blood lead measurements reflect a compromise between convenience and accuracy. Other indices, such as dose or equivalence of effect may be less reliable and may make comparison between different studies difficult.

There have been some studies attempting to link normal or drug-induced behaviour with brain neurochemistry. As yet these studies have largely failed to relate behavioural changes [36, 40] to altered neurochemistry, although one report [27] has shown a limited correlation.

Conclusions

The past decade has seen extensive investigation into the effects of lead on several aspects of catecholaminergic function. Given the resources devoted to this topic it is disappointing how little can be concluded. In broad terms, however, it can be stated that two distinct types of lead effect have been reported.

The first of these is shown mainly in the earlier studies, where relatively large exposures of lead were employed, causing a variety of changes. In these studies catecholaminergic function was found generally to be inhibited, perhaps as a result of nonspecific effects of lead, including general toxicity and undernutrition.

The second type of effect has been seen in studies utilizing relatively small doses of lead and monitoring lead load by measuring blood lead levels. The results of these studies are harder to interpret, but overall they suggest a stimulation of catecholaminergic function at levels of lead comparable to those found in exposed humans. The results of low-dose experiments in which drug-elicited behaviour is studied are of particular importance in the context of borderline effects.

At the cellular level, the mechanism of the action of lead has also received much attention. Since high doses of lead induce nonspecific nutritional effects, it is possible to infer that similar changes may occur at lower levels of exposure. Bull [42] reported inhibition of energy metabolism in the offspring of rats dosed with 200 ppm Pb (as the chloride) till weaning, in which blood leads ranged up to 36 μg Pb/100 ml. From this, it could be concluded that the various biochemical changes produced by lead are nonspecific, and the result of impaired metabolic processes and pathways. However, lead is also likely to interfere with physiologically important cations, notably calcium. Lead antagonizes this ion [43] and Wince *et al.* [21] point out that the inhibitory action of lead on neurotransmitter release may be a consequence of this and therefore nonspecific.

The action of lead in catecholaminergic neurones, however, seems to be better established, as sequestration of lead in mitochondria has been shown to interfere with transmitter release. In normal neurones a net influx of calcium down an external/internal concentration gradient in nerve terminals occurs upon depolarization. This is buffered by calcium release from mitochondria and a normal calcium-dependent neurotransmitter release occurs. However, in neurons containing lead the presence of lead in the mitochondria inhibits mitochondrial calcium release and the external/internal gradient is not reduced. Relatively more external calcium enters the neurone causing a net increase in calcium-dependent neurotransmitter release [44]. This is therefore a specific lead catecholaminergic effect and such an alteration may produce further changes in neurotransmitter turnover, reuptake and post-junctional mechanisms.

The susceptibility of biopterin metabolism to levels of lead within the normal human range has important implications for aminergic processes; and the variable response to lead in functionally different CNS regions reported by Govoni and colleagues indicates that catecholamine chemistry is variably affected at several distinct loci.

To summarize, the links between lead and hyperactivity, initially the focus of interest for investigation of the neurochemical alterations induced by lead, remain ambiguous. However, the interaction between lead and catecholaminergic function appears to be better understood and although further work is required to resolve the nature of this interaction, available evidence points to the existence of a catecholaminergic dysfunction at levels of lead relevant to human childhood exposure.

Acknowledgements—The author would like to thank Drs N. G. Carmichael, P. D. Lewis and P. Willner for helpful criticism. The author is supported by grants from the Wellcome Trust and the Health and Safety Executive.

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