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COMMENTARY

MONOAMINE METABOLITES: THEIR RELATIONSHIP AND LACK OF RELATIONSHIP TO MONOAMINERGIC NEURONAL ACTIVITY

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Among the three generally accepted classes of central neurotransmitters, the monoamines [dopamine (DA), norepinephrine (NE), epinephrine (E) and serotonin (5-HT)], acetylcholine (ACh), and the amino acids (γ-aminobutyric acid, glutamic acid, aspartic acid and glycine), the monoamines are chemically unique in one respect. It is thought that a fraction (ΔF) of the released monoamine is metabolized (probably both intraneuronally and extraneuronally) during the release–reuptake cycle. These metabolic products do not re-enter the transmitter synthetic pathway. For example, DA is metabolized to dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 3-methoxytyramine (3-MT), none of which re-enters the DA synthetic pathway. Instead, during periods of enhanced release, steady-state concentrations of DA are maintained by new precursor molecules (tyrosine) entering the synthetic pathway. In dopaminergic neurons at least, the mechanisms that mediate the enhanced synthesis appear to operate through changes in the kinetics of the rate-limiting enzyme tyrosine hydroxylase [1]. Neuroscientists have, for some time now, utilized this chemical property of monoaminergic nerves as an indirect way of assessing their neurophysiological activity. The basic assumption, never explicitly stated, can probably be summarized as follows:

(1) $M_t \propto n$

(2) $M_t = n \cdot \Delta F$

where M_t = the molar (M) quantity of metabolite produced in time t, n = the number of release cycles, and ΔF = the fraction of released transmitter trapped in each release cycle. It follows from the above that:

$$n \propto n \cdot \Delta F$$

In actual experiments, an additional factor would be required to correct for the fraction of metabolite that is transported away from its site of production in time t, but this is merely a detail. In short, wittingly or unwittingly, changes in monoamine metabolite levels have come to be equated with changes in monoaminergic neuronal activity. That is, a purely neurochemical measure has come to be equated with a neurophysiological response. In the process, certain variations of the basic theme have been developed.

The T/M ratio

Since monoamine levels remain fairly constant during periods of enhanced release, a decrease in the transmitter (T) to metabolite (M) ratio has been assumed to be indicative of an increased turnover of the transmitter, and this, in turn, is equated with increased neuronal activity [2, 3].

CSF, plasma and urine metabolite levels as indices of central neuronal activity

Again, following the formulation that metabolites are produced in the release–reuptake cycle, and knowing that transport mechanisms exist for the removal of monoamine metabolites away from their site of production [4], a fairly general assumption has been made that levels of these metabolites in the CSF, plasma and urine are at least a working reflection of central neuronal activity [5–7]. The obvious necessity of having to use non-invasive methods to try to elucidate the mechanism of action of centrally-acting drugs in clinical studies has lead to a liberal application of this reasoning in clinical studies and models of clinical cases [8–11].

The main question posed in this short review is whether the basic assumption itself, that monoamine metabolite levels are always an accurate reflection of monoaminergic neuronal activity, is a justifiable assumption. This question is really a particular aspect of a broader general question related to the use of transmitter turnover studies as a reflection of neuronal activity. However, this broader question will not be dealt with further in this review (but see Refs. 12 and 13).

In the strictest sense, monoamine metabolite levels would be a reflection of monoaminergic neuronal activity under the following conditions:
(1) If transmitter metabolism were only, and always coupled to transmitter release.
(2) If the drugs used in purely pharmacological studies did not stimulate transmitter synthesis and/or metabolism independently of release.
(3) If the experimental procedures (drugs used) did not impede or accelerate the removal of the metabolites from their sites of production.
(4) If the factors that govern the reuptake and resequestering of monoamines into the Ca^{2+}-dependent releasable pool remained unchanged during the experiment.

Therefore, intraneuronal transmitter metabolism that is unrelated to release, and blockade of the transport of metabolites from their site of production are two of the more obvious factors that would give false positive results. We shall now examine specific instances in which:
(1) the hypothesis is almost certainly valid, and (2) the hypothesis is almost certainly wrong.

Valid cases

Electrical stimulation studies. Several investigators, working in different regions of the CNS have demonstrated that monoamine synthesis and metabolism are increased in response to electrical stimulation of the appropriate monoaminergic pathways [14–16]. In general, also, the observed increases are proportional to the duration and/or intensity of stimulation [16]. Therefore, the idea that monoamine metabolite levels are sometimes increased during enhanced monoaminergic neuronal activity seems certain. Even in this simplest case, however, there is some doubt. In almost all of the studies concerned, the anaesthetic used was chloral hydrate (usually 400 mg/kg, i.p.). Furthermore, chloral hydrate itself causes an increase in the activity of tyrosine hydroxylase [1] (the K_m for tyrosine is reduced), and an increase in the levels of DOPAC and HVA in the striatum and spinal cord [15, 17]. In an attempt to clarify this problem, this author recently carried out some experiments in which the left substantia nigra was stimulated (15 Hz, 15 min) using three anaesthetics; Brietal (55 mg/kg, i.p.), urethane (1.5 g/kg, i.p.) and chloral hydrate (400 mg/kg, i.p.). Only in the chloral hydrate group were DOPAC and HVA significantly increased on the stimulated side (unpublished observation). But, even if it were quite certain that the metabolites increased linearly with the intensity of electrical stimulation, independently of the anaesthetic used, the results would hardly be interesting. In this case, the experimental variable, namely neuronal activity, is usually the unknown factor in the majority of the more usual cases.

Questionable cases

Antipsychotic drugs and dopaminergic activity. Two common effects of the most frequently used antipsychotic drugs (e.g. haloperidol and chlorpromazine) are: (1) blockade of the dopamine receptor [18], and (2) an increase in the levels of DOPAC and HVA in the CNS. It is commonly thought that these two effects are linked. Blockade of the postsynaptic DA receptor probably activates, by a negative feedback mechanism (the precise details of which are unknown), the presynaptic dopamine neurone [19]. Hence, the increases in DOPAC and HVA. Such an activation has also been demonstrated electrophysiologically [17]. Nevertheless, it is now known that haloperidol inhibits the transport of DOPAC and HVA away from their site of production [20, 21]. Moleman *et al.* [20] were among the first to demonstrate this fact and, in commenting on their results, noted that: "A basic assumption in such studies is that alterations in metabolite concentrations reflect alterations in functional activity of dopaminergic neurons . . . haloperidol strongly inhibits the transport or disappearance of acidic dopamine metabolites HVA and DOPAC from the rat striatum". Westerink *et al.* [21] have recently confirmed this observation, reporting that haloperidol significantly decreased the fractional rate constant for the decline of HVA in the striatum after the administration of the MAO inhibitor pargyline. These latter authors were also moved to issue a caution that: "these findings strongly suggest that great care should be taken when drug-induced alterations in DOPAC and HVA concentrations are interpreted as changes in dopaminergic activity".

Production of metabolites in the absence of nerve terminals and nerve activity. Large quantities of DA and NE are synthesized in the developing spinal cord, as well as in the cord of the young adult, after the administration of the catecholamine precursors (L-dihydroxyphenylalanine (L-DOPA) or tyrosine [22, 23]. Moreover, the large quantities of transmitter synthesized are also effectively metabolized [24]. In the spinal cord, when the monoaminergic nerve terminals were destroyed by transection of the cord, or by the use of the neurotoxins 6-hydroxydopamine (6-OHDA) and 5,7-dihydroxytryptamine (5,7-DHT), the synthesis and metabolism of DA (but not of NE) persisted [22, 24]. Indeed, in some cases the concentrations of DOPAC and HVA equalled the levels in the intact spinal cord. These results suggest that DA can be synthesized and metabolized in elements other than monoaminergic neurons—probably in glia, non-catecholaminergic cell bodies, and non-monoaminergic nerve terminals. Sharman [35] long ago reported that a wide variety of drugs all increased the metabolism of DA in the brain, but produced different behavioural effects. Therefore, he argued, "the fact of the increased DA metabolism was unlikely to be the common denominator of the observed behaviours. Again, γ-hydroxybutyrate has been shown to block impulse traffic in the nigro-striated pathway, but to increase significantly the synthesis (and almost certainly the metabolism) of DA in the striatum [26, 27]. Therefore, increased nerve activity is not a necessary precondition for the increased synthesis of DA. Even insulin has been found to increase the levels of HVA and 5-hydroxyindoleacetic acid (5-HIAA) in the brain [28]. On the basis of the above observations, it must now be accepted that the synthesis and metabolism of DA can be increased in the CNS under conditions that are almost certainly not related to increases in impulse traffic in dopaminergic neurons. This general observation almost certainly holds for noradrenergic and serotonergic neurons as well. What seems to be quite certain, as this author has stressed before [22], is that the metabolism of monoamines is very tightly coupled to their synthesis. But synthesis may or may not be coupled to nerve activity. Only when synthesis is coupled to nerve activity can metabolite production be used as an index of neuronal activity, but not otherwise. We now arrive at the crux of the matter, the fact of intraneuronal metabolism of monoamines that is probably unrelated to either transmitter release or nerve activity. This important problem has been mentioned by several authors [25, 29] in the past, and will be dealt with in the discussion.

It is appropriate to end this section by a consideration of 3-MT. Since it is accepted that the O-methylating enzyme COMT (catechol-*O*-methyltransferase) is located mainly extra-neuronally [30], several authors have proposed that 3-MT is the metabolite that would reflect DA release most accurately [29, 31–33]. Now it appears that even this plausible suggestion is open to reasonable doubt. It was shown recently [34] that 3-MT is increased significantly in the striatum after microwave radiation (heat), but that the levels are decreased after such radiation, followed by cooling of the brain on ice before dissection. The authors argued that 3-MT is normally present in very insignificant amounts in the brain, and that the levels measured in experiments are a reflection principally of the method of preparation of the tissue for analysis and, therefore, bear little or no relationship to the release of DA under physiological conditions *in situ*.

Morphine and 5-HIAA levels. Several lines of evidence have converged in recent years to support the idea that at least a component of morphine-mediated analgesia is caused by an activation of the descending raphe-spinal system from the nucleus raphe magnus [35]. In keeping with this hypothesis, several authors have shown that after the systemic administration of morphine, or electrical stimulation of the nucleus raphe magnus, the synthesis and metabolism of 5-HT in the dorsal horn of the spinal cord are increased [36–39]. In keeping with current thinking, some authors have assumed that increases in 5-HIAA are a reflection of an increased turnover rate of 5-HT and this, in turn, an indication of increased serotonergic neuronal activity [3, 40]. The published evidence is unequivocal in the demonstration that morphine causes an increased synthesis and metabolism of 5-HT in virtually all areas of the CNS with a serotonergic innervation, regardless of whether or not such areas are associated with pain [3, 41]. In the spinal cord, for example, morphine causes significant increases in 5-HIAA in all the major functional regions of the spinal cord sensory (dorsal horn), autonomic (zona intermedia) and somatic motor (ventral horn) [41]. The response is not principally associated with the dorsal horn, as one might expect. Similarly in the brain, Snelgar and Vogt [3] have shown that morphine causes an increase in the concentration of 5-HIAA in widely scattered parts of the CNS. In some of these areas, e.g. the striatum, microinjected morphine causes an increase in 5-HIAA with no effect on pain threshold [42]. Alternatively, morphine, when microinjected into the aqueduct causes profound analgesia with no change in spinal cord 5-HIAA. In virtually all of these experiments, there has been no direct evidence that morphine causes an increase in the release of 5-HT. In the absence of such evidence, the conclusion must be that morphine, by an unknown mechanism, can increase the intraneuronal synthesis and metabolism of 5-HT. The evidence for a causal relationship between this neurochemical effect of morphine and the mechanism of morphine-induced analgesia is not compelling, despite the wealth of published data. Very recently, it was shown that the nucleus raphe magnus is not required for the relay of the antinociceptive effect induced by stimulation of the midbrain periaqueductal gray region [43], as is commonly believed. Moreover, intrathecal morphine causes analgesia without increasing spinal cord 5-HIAA, and morphine, when administered intrathecally, still causes analgesia in animals with a 90% depletion of the spinal cord 5-HT [44].

Discussion

For clarity, the points in the discussion will be itemized.

(1) *Monoamine metabolites: What certain information do they convey?* In the normal untreated animal, monoamine metabolites are an indication of the metabolic intactness of monoaminergic neurons [45]. Under experimental conditions, 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) and 3,4-dihydroxyphenylethyleneglycol (DHPG) reflect the *metabolic functioning* of noradrenergic neurons [46–48], since NE is synthesized exclusively in noradrenergic neurons [22].

(2) *The link between synthesis and metabolism.* Recent studies in the spinal cord have suggested that NE is normally present at a concentration of about 50% of the maximum holding capacity of the nerve [22]. Synthesis may be stimulated, for example, by the administration of precursor (L-DOPA or tyrosine). But, the newly synthesized transmitter is immediately metabolized [24, 46], and the levels of NE remain constant, while the concentration of MHPG increases. There is no definitive evidence that the newly synthesized transmitter is released before it is metabolized. But, indirect inferences from neurophysiological studies suggest that some of it may be released [49]. The scheme outlined above for noradrenergic neurons seems to hold for dopaminergic and serotonergic neurons in the spinal cord, and perhaps the brain as well.

(3) *Synthesis and metabolism of DA in non-monoaminergic elements.* It has been demonstrated in both the spinal cord and the brain that DA can be synthesized in very large amounts from its precursors, L-DOPA or tyrosine [22, 50, 51], and that the newly-synthesized DA is efficiently metabolized to DOPAC and HVA [24]. Moreover, both synthesis and metabolism of DA persist to a considerable degree, after the destruction of monoaminergic nerves [22, 50]. Therefore, DA can be synthesized and metabolized in large amounts in non-monoaminergic elements. Other neuronal cell bodies, nerve terminals, the endothelial lining of capillaries and possibly glia are all likely sites of DA synthesis and metabolism. It would seem likely that the synthesis and metabolism of 5-HT can occur under the same conditions as described for DA.

(4) *The reality of intraneuronal metabolism of monoamines.* Over the years, several authors have alluded to the possibility of intraneuronal metabolism of monoamines that is unrelated to release [25, 29]. In the case of DA, when increases in DOPAC occur with no corresponding increases in HVA, as sometimes occurs in response to chloral hydrate (see Table 2, Ref. 15) and other drugs, the indication is almost certainly of a pure case of intraneuronal metabolism of DA that is unrelated to release. Similarly, the increases in DHPG and DOPAC, reported after the administration of L-

DOPA or tyrosine, point towards the intraneuronal metabolism of NE [52, 53].

(5) *Release: The missing factor.* In most of the studies cited in this review, the most important missing parameter has been release. It is certain that, in experiments involving electrical stimulation, there is both increased release and metabolism. To this author, it would seem that the fundamental mistake that has been made lay in assuming the converse, namely that when there was increased metabolism, it was indicative of increased release. The motivation for this assumption is obvious. It is the necessity of having to draw conclusions about function (neuronal firing) on the basis of indirect, primarily pharmacological/neurochemical evidence [54]. Judging from the very wide variety of situations in which the assumption has been made, it would seem that it is a fairly widely accepted working hypothesis. The situation is, of course, not hopeless. It requires that researchers should recognize that metabolite studies alone cannot be used as the sole criterion of a neurophysiological functional correlate. In the future, release studies and the electrophysiological monitoring of nerve activity are likely to assume more significant roles in neurotransmitter studies.

(6) *Increased turnover and efficient reuptake.* In retrospect, it seems reasonable to ask whether these two efficient mechanisms are required to conserve transmitter stores during enhanced nerve activity. There is no easy answer to this question. But, given the waste of energy that these two processes would entail towards achieving the same end (making transmitter available for chemical neurotransmission), reasonable doubt can at least be entertained about the relative importance of increased turnover in monoaminergic neurons as a physiological requirement to maintain neurotransmission. In the peripheral nervous system, neuronal reuptake has been estimated at about 95% [55]. What, then, is the true significance of increased turnover in monoaminergic nerves? The answer must be for the present that one is not quite sure. In cholinergic neurons, and neurons utilizing amino acids as their transmitters, the significance of increased turnover during enhanced nerve activity is obvious. True, in monoaminergic nerves some increase in synthesis/turnover is essential to make up the fraction (ΔF) of the transmitter that is trapped during the release/reuptake cycle. But, this is unlikely to account fully for the fairly large increases that have been reported, especially in some purely pharmacological experiments. But, conversely, enhanced dopamine synthesis can be demonstrated when impulse traffic in the nerves has ceased [26, 27]. Increased synthesis and metabolism of monoamines can be purely pharmacological responses, with little or no relationship to the functional requirement of the nerve.

Concluding remarks

The main purpose of this short review has been to raise a question concerning the use of monoamine metabolites as indices of monoaminergic neurophysiological activity. There are many other situations, not dealt with directly, in which monoamine metabolites are used as indices of monoaminergic neuronal activity [56–64]. It was also pointed out that this query is an aspect of a more general question concerning the use of neurotransmitter turnover studies as indices of physiological nerve activity. It is difficult to reach definitive conclusions. Nevertheless, two points are important. One is that, in the absence of any evidence of release, the significance of increased metabolite levels alone may be of limited functional importance. The second is that intraneuronal metabolism of monoamines unrelated to release appears to be an established fact. Therefore, increased monoamine metabolites may not always be indicative of increased neuronal activity. We are now led back to the original question, but now posed without assuming that the answer is easy or obvious. What can changes in monoamine metabolites tell us about the physiological functioning of monoaminergic nerves?.In addition, one could now also pose the question concerning the meaning of increased intraneuronal metabolism unrelated to release. What is the significance of this phenomenon? Indeed, in view of reports showing the electrophysiological effects of intracellularly injected monoamines [65], the complex effects on cortical neuron excitability of iontophoretic DA [66] and the presence of the decarboxylase enzyme in non-monoaminergic neurons in the CNS [67], one could ask: do monoamines (and especially DA) have real intracellular physiological effects which have been so far ignored? And lastly, in the worst case, it is possible to imagine a situation in which the increased synthesis and metabolism of monoamines that occur under purely pharmacological conditions result simply from processes that increase substrate availability. If the synthetic enzymes are unsaturated with their substrates, synthesis would ensue (after L-DOPA or tyrosine, the synthesis and metabolism of NE are greatly enhanced). It is possible that this newly synthesized transmitter could be metabolized without ever mixing with the Ca^{2+}-dependent, physiologically important, releasable pool. This is a depressing conclusion, but is, nevertheless, a real possibility. In the future, the application of mass spectrometric and isotope dilution techniques could provide us with answers to some of these questions.

Addendum—A recent report by Pickar *et al.* [68] is typical of the problem raised in this review. These authors found that plasma HVA levels were reduced in schizophrenic patients in response to fluphenazine (a phenothiazine neuroleptic) treatment. Further, there was a significant correlation between the fall in plasma HVA and the improvement in the psychotic state of the patients. The main conclusion was that fluphanazine probably decreased the firing of dopaminergic neurons in the CNS. Hence, a reduction in the turnover rate of DA, and a consequent fall in plasma HVA. This interpretation follows the traditional line of thought. An equally valid explanation is simply that fluphenazine blocked the transport of HVA from the brain. Hence, HVA levels would rise in the brain, and fall in the plasma. No change in the firing of dopaminergic neurons, or in the turnover rate of DA is required to achieve these effects.

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