On the concentration of 5-hydroxyindoleacetic acid in schizophrenia: A meta-analysis

Henry C. Tuckwell*, James A. Koziol

*School of Mathematical Sciences, Stochastic Analysis Group, Australian National University, Canberra, ACT 0200, Australia

bScripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA

Received 31 October 1994; revision received 9 June 1995; accepted 3 September 1995

Abstract

A meta-analysis was performed on the results of a number of investigations of concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid, serum, or urine of acute and chronic schizophrenic patients. Only those studies were chosen in which some degree of age and gender matching were achieved and in which the comparison subjects were healthy normal volunteers. Fisher's procedure and a weighted Liptak method revealed no significant differences between normal subjects and schizophrenic patients, indicating that disturbances of serotonergic turnover do not, in general or essentially, contribute to the etiology of schizophrenia.

Keywords: Serotonin; Statistical analysis

1. Introduction

A number of hypotheses have been advanced to explain the differences between the functioning of the brains of normal and schizophrenic individuals. These include viral insults, neuroreceptor disturbances, neurodevelopmental disorders (Hudson et al., 1993), structural changes in brain regions such as the frontal cortex (Winn, 1994), and disturbances in many neurotransmitter systems including dopamine, serotonin, acetylcholine and y-aminobutyric acid (McGeer et al., 1987). However, research into the etiology of schizophrenia has been dominated for several decades by the dopamine hypothesis, which holds that certain populations of dopaminergic neurons, particularly those in the striatum, are hyperactive (for reviews, see Meltzer and Stahl, 1976; Haracz, 1982; Widerlöv, 1988; Heritch, 1990).

Some investigations have focused on post-mortem examinations of dopamine distribution, but most of the supporting evidence for the dopamine hypothesis has come from pharmacological studies. The cornerstone of the theory has been the correlation between the antipsychotic efficacy of neuroleptic drugs and their ability to block dopamine D2 receptors. It has been observed that some antipsychotic medications can lead to a 70–90% occupancy of striatal dopamine...
D₂ receptors (Nordström et al., 1992). In addition, it has been found that certain drugs that increase dopaminergic activity may worsen schizophrenic symptoms (Davis et al., 1991).

One approach to the examination of the dopamine hypothesis has been to focus on its major metabolite, homovanillic acid (HVA). We recently performed a meta-analysis of the concentrations of HVA in the cerebrospinal and other body fluids. In this approach, the results of disparate studies designed to investigate the possibility of hyperdopaminergic activity in schizophrenic patients relative to normal subjects can be combined (Tuckwell and Koziol, 1993). The underlying principle is that an excess accumulation of a metabolite of a neuroamine transmitter indicates an increase in the activity of neurons that use that transmitter (Cooper et al., 1991). We ascertained that there is little evidence to support the general claim of an elevation of HVA levels in schizophrenia, as would perhaps be expected from the dopamine hypothesis. Rather, the results obtained suggest that HVA levels in schizophrenic patients are equal to or indeed even lower than those in normal subjects. However, the claim that HVA levels are not altered in schizophrenia does not necessarily mean that the dopaminergic system is not disturbed. Rather, metabolite levels pertaining to a given neurotransmitter probably reflect only the state of presynaptic processes of synthesis and release.

In addition to the dopamine hypothesis of schizophrenia, there has long been interest in the possibility of a disturbance in the serotonergic system, inferred from the results of Woolley and Shaw (1954) on the hallucinatory effects of LSD; for a discussion, see Öhlin et al. (1992). Many studies have examined the role of serotonin in schizophrenia, usually through the examination of the concentration of 5-hydroxyindoleacetic acid (5HIAA), the principal metabolite of serotonin. In one such study, by Ågren et al. (1986), a significant correlation was found between the levels of HVA and 5HIAA in the cerebrospinal fluid (CSF), indicating a possible functional interaction between central nervous system (CNS) dopaminergic and serotonergic systems (Pickar et al., 1990). Some authors have found a positive correlation between positive symptoms of schizophrenia (for example, hallucinations and grandiosity) and levels of 5HIAA (Gattaz et al., 1982), whereas others have found a similar correlation with such symptoms as emotional withdrawal and poor cognitive performance (Csernansky et al., 1990).

In the present report, a combined analysis of several sets of results from studies of 5HIAA was performed. This approach has previously proved useful in psychiatric research. It was used, for example, by Van Horn and McManus (1992), who were interested in establishing if there were significant brain ventricular size differences between schizophrenic patients and normal subjects. One clear advantage of combining the results of several studies is the effective increase in sample size. In particular, we will examine whether 5HIAA levels in CSF, serum, and urine are increased in schizophrenic patients relative to comparison subjects.

2. Methods

We obtained data from several articles summarized previously by Heritch (1990) and supplemented by a Medline search for related works. We included only studies that included a drug-free period ≥ 1 week before the measurement of 5HIAA levels and a group of normal subjects comparable to the patient group with respect to age and gender (for a discussion of the importance of age and sex matching in neurochemical investigations, see Gerner et al. [1984]). These criteria resulted in the exclusion of many studies from the meta-analysis. (For example, the study of Gattaz et al. [1982] did not qualify for inclusion because their comparison group did not consist of normal subjects but instead of subjects with nonspecific neurological symptoms.) Table 1 lists the studies that were included and the subtype(s) of schizophrenia included in each (acute, chronic, or both subtypes).

There are several statistical approaches to the combination of results from different experiments designed to measure the same variable or effect (e.g., see Hedges and Olkin [1985]). In the present study, we used two nonparametric approaches: (1) Fisher's combination procedure and (2) a modification of Lipták's procedure. Let $P$ denote a ran-
dom variable representing the significance probability, or attained significance level, of an experimentally obtained test statistic. Typically, if the underlying test statistic is continuous and the null hypothesis is true, then \( P \) is uniformly distributed on the interval \((0,1)\). We now consider independent experiments, with one-sided significance probabilities \( P_1, P_2, \ldots, P_n \). Fisher's combination procedure is based on the statistic:

\[
C = -2 \sum_{i=1}^{n} \log (P_i);
\]

In a weighted Lipták procedure (Koziol and Tuckwell, 1994) with weights \( w_i > 0 \), we employ the statistic:

\[
L_w = \frac{-\sum_{i=1}^{n} w_i \Phi^{-1}(P_i)}{\sqrt{\sum_{i=1}^{n} w_i^2}}
\]

where \( \Phi^{-1}(-) \) is the inverse of the normal distribution function. The value of \( \Phi^{-1}(P_i) \) is the \( z \) score, or value of a standard normal random variable \( Z \), such that the probability of a value of \( Z \) less than \( z \) is in fact \( P_i \); that is, if

\[
Pr \{ Z < z \} = P_i,
\]

then \( z = \Phi^{-1}(P) \). The weight factors are introduced to represent more accurately the contributions from experiments that yield statistics of different efficiencies. Under the null hypothesis that \( P_i \) is uniformly distributed on \((0,1)\), Fisher's combination statistic \( C \) has a \( \chi^2 \) distribution with \( 2n \) degrees of freedom, and the test statistic for the weighted Lipták procedure has a standard normal distribution. Large values of \( C \), or of \( L_w \), are considered to be evidence against the null hypothesis.

3. Results

We extracted information about 5HIAA levels in the schizophrenic and normal groups from each of the 12 studies that met criteria for inclusion in the analysis (see Table 1). Serum levels of 5HIAA were measured in pmol/ml; CSF levels, in pmol/ml or ng/ml; and 24-h urine values, in mmol/day.

The effect size for the \( j \)-th study is the standardized mean difference,

\[
d = \frac{\bar{X}_E - \bar{X}_C}{s},
\]

where \( \bar{X}_E \) and \( \bar{X}_C \) are the sample means of the outcome variable for the schizophrenic and nor-

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Outcome</th>
<th>Effect size</th>
<th>( n_E )</th>
<th>( n_C )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfredsson and Wiesel (1989)</td>
<td>Acute</td>
<td>Serum</td>
<td>-0.442</td>
<td>23</td>
<td>10</td>
<td>0.874</td>
</tr>
<tr>
<td>Berger et al. (1980)</td>
<td>Acute</td>
<td>CSF</td>
<td>-0.302</td>
<td>9</td>
<td>23</td>
<td>0.776</td>
</tr>
<tr>
<td>Csernansky et al. (1990)</td>
<td>Chronic</td>
<td>CSF</td>
<td>0.151</td>
<td>21</td>
<td>9</td>
<td>0.354</td>
</tr>
<tr>
<td>Gernser et al. (1984)</td>
<td>Chronic</td>
<td>CSF</td>
<td>0.281</td>
<td>20</td>
<td>37</td>
<td>0.158</td>
</tr>
<tr>
<td>Karoum et al. (1987)</td>
<td>Chronic</td>
<td>24-h urine</td>
<td>-0.149</td>
<td>20</td>
<td>16</td>
<td>0.670</td>
</tr>
<tr>
<td>Lewine et al. (1991)</td>
<td>Chronic</td>
<td>CSF</td>
<td>0.189</td>
<td>45</td>
<td>91</td>
<td>0.151</td>
</tr>
<tr>
<td>Lindström (1985)</td>
<td>Acute</td>
<td>CSF</td>
<td>0.085</td>
<td>40</td>
<td>21</td>
<td>0.377</td>
</tr>
<tr>
<td>Lindström et al. (1990)</td>
<td>Acute</td>
<td>CSF</td>
<td>0.263</td>
<td>24</td>
<td>47</td>
<td>0.149</td>
</tr>
<tr>
<td>Nybäck et al. (1983)</td>
<td>Acute</td>
<td>CSF</td>
<td>0.182</td>
<td>15</td>
<td>47</td>
<td>0.270</td>
</tr>
<tr>
<td>Öhlund et al. (1992)</td>
<td>Acute</td>
<td>CSF</td>
<td>0.0</td>
<td>36</td>
<td>43</td>
<td>0.500</td>
</tr>
<tr>
<td>Pickar et al. (1990)</td>
<td>Chronic</td>
<td>CSF</td>
<td>0.045</td>
<td>26</td>
<td>23</td>
<td>0.438</td>
</tr>
<tr>
<td>Post et al. (1975)</td>
<td>Acute</td>
<td>CSF</td>
<td>0.024</td>
<td>22</td>
<td>33</td>
<td>0.465</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.057</td>
<td>20</td>
<td>10</td>
<td>0.442</td>
</tr>
</tbody>
</table>
normal groups, with sample sizes $n_E$ and $n_C$ respectively, in the $j$-th study, and $s$ is the pooled sample standard deviation

$$s = \sqrt{\frac{(n_E - 1) s_E^2 + (n_C - 1) s_C^2}{n_E + n_C - 2}}.$$

The $P$ value is the one-sided exceedance probability for the statistic $d$ upon reference to a central $t$ sampling distribution; that is,

$$P = Pr\left( T \geq \sqrt{\frac{n_E n_C}{n_E + n_C}} d, T \sim t_{n_E + n_C - 2}. \right)$$

We classified the experimental findings in Table 1 into the following three categories of patient types: acute schizophrenia, chronic schizophrenia, and both subtypes. Within each category, we computed the values of the two combination statistics given in the previous section, assessing the null hypothesis of no difference in 5HIAA levels between patients and normal subjects versus the alternative that 5HIAA levels would be elevated in patient groups relative to normal groups. In this regard, for the weighted Lipták procedure, we weighted the contribution of the $j$-th study by its value of

$$w = \sqrt{\frac{n_E n_C}{n_E + n_C}},$$

the inverse of the standard deviation of the effect size for that study; see Koziol and Tuckwell (1994) for further discussion.

Note that the statistic $C$ has degrees of freedom determined by the number of experiments whereas each experiment yields a $t$ statistic with its own degrees of freedom. The statistic $L_w$ has a standard normal distribution, and hence it has no associated degrees of freedom.

For the acute category, the value of Fisher's statistic is $11.21$ ($n = 7, df = 14$) whereas the value of the modified Lipták statistic is $0.145$, with corresponding $P$ values of $0.67$ and $0.44$, respectively. For the chronic category, Fisher's statistic returned a value of $14.50$ ($n = 6, df = 12$) while Lipták's $L_w$ was $1.240$, with $P$ values of $0.27$ and $0.11$, respectively. For the combined groups, we have $C = 25.70$ ($n = 13, df = 26$) and $L_w = 0.991$, with corresponding $P$ values of $0.48$ and $0.16$, respectively.

From this analysis we see that there is no evidence to suggest that 5HIAA levels are increased in schizophrenia, whether in an acute phase, a chronic phase, or either of these phases. Further analysis revealed that there is also no evidence of diminished 5HIAA levels in schizophrenia. We note that in none of the individual studies was there evidence that 5HIAA levels were altered in patients versus normal subjects. However, one cannot conclude from the individual results that the combination of all the results would lead to the same conclusion — a principle that highlights the potential importance of meta-analysis. Nevertheless, despite the fact that the studies included in the meta-analysis were of comparable and acceptable quality, there is a possibility of a type II error.

4. Discussion

We have synthesized the results from several diverse studies in which 5HIAA levels were measured in groups of schizophrenic patients and compared with those in age- and gender-matched normal subjects. Our analysis revealed that there were no significant differences in 5HIAA levels, making it unlikely that disturbances of the turnover of serotonin contribute in an essential or fundamental way to schizophrenia. This could be interpreted further by concluding that serotonin synthesis and release are not changed, but there may be compensating factors.

One factor that makes it difficult to draw conclusions from studies of neurochemical disturbances in psychiatric patients is that the usual classification scheme (e.g., DSM-III, DSM-IV) is based on the presence of groups of behavioral manifestations or patterns that have broad rather than narrow limits and that are not necessarily relevant to etiology. Since the validity of the diagnosis of schizophrenia is uncertain, peripheral indicators of brain neurochemistry would be unlikely to differ from those of normal subjects in a consistent or precise fashion. It is not surprising therefore that some investigators have found that certain subtypes of schizophrenia may have altered
serotonergic functioning, even though this is not the case for schizophrenia in general.

We may further illustrate this source of difficulty with some historical evidence: Serotonergic activity has long been thought to be disturbed in depressed patients, as evidenced by the finding of lowered 5HIAA levels (Ashcroft and Sharman, 1960). This property was later refined to include only patients suffering from ‘type B’ depression, characterized by: (i) normal or high levels of the chief noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG); (ii) favorable response to amitriptyline; (iii) lack of mood change in response to d-amphetamine; (iv) decrease in MHPG after administration of desipramine; and (v) lack of response to imipramine (Maas, 1975). Hence, if a patient classified as schizophrenic also had some symptoms of ‘type B’ depression, it would not be surprising to find a serotonergic disturbance, even if it were not a primary manifestation of schizophrenia. This is corroborated by some of the findings mentioned in the Introduction, namely that certain subsets of schizophrenic patients with certain behavioral characteristics tend to have abnormal levels of 5HIAA.

However, the results of the present meta-analysis indicate that the core symptomatology of schizophrenia is not accompanied by altered levels of 5HIAA and hence does not involve significant alterations in the presynaptic biochemistry of central serotonergic neurons. This conclusion is not made less tenable by the finding of Ågren et al. (1986) of a correlation between HVA and 5HIAA in schizophrenia, because as we have shown in our previous study, alterations in HVA in schizophrenia are unlikely to be significant. We note that this correlation has been claimed to be always present by Pickar et al. (1990), and hence that there was a ‘functional interaction’ between dopaminergic and serotonergic systems within the CNS. However, several of the reports reviewed by Widerlöv (1988) did not show such a correlation. The fact that some schizophrenic subgroups tend to show evidence of altered levels of 5HIAA may suggest that individuals in such subgroups are subject to multiple pathological conditions and, in particular, show biochemical evidence of depression. Notwithstanding the fact that 5HIAA levels are not significantly altered in schizophrenia, Kahn et al. (1992) have concluded that there is a serotonin receptor dysfunction in this disorder.

References


