ACCUMULATION AND METABOLISM OF PIPECOLIC ACID IN THE BRAIN AND OTHER ORGANS OF THE MOUSE

H. NISHIO¹, J. ORTIZ, AND E. GIACOBINI²

Laboratory of Neuropsychopharmacology
Department of Biobehavioral Sciences
University of Connecticut
Storrs, Connecticut 06268

Accepted June 19, 1981

The long-term accumulation of pipecolic acid, as well as its disappearance following exogenous administration was studied in brain and other organs of the mouse. Mice were pulse-injected intraperitoneally or intravenously with 1 µCi [³H] D,L-pipecolic acid (6.9 nmol/mouse = 2.9 µg/kg). The total radioactivity retained in tissues was measured in brain, liver, and kidney, as well as in plasma during the period 1 min to 24 hr. TLC separation of DNP-derivatives was performed. Three features of the pattern of retention of pipecolic acid are most salient; first the rapid accumulation in brain, second the rapid secretion of this compound in the urine, and third the long-lasting steady levels of radioactivity maintained in brain.

Sixty minutes after i.v. injection, the brain/plasma ratio is approximately 0.2 and approaches unity only at 5 hr. Following intraperitoneal injection the percent recovered as pipecolic acid in brain is 78% at 30 min and 71% at 120 min, suggesting a slow metabolic activity. Liver shows a different trend than brain with a slower accumulation and a faster disappearance. Kidney shows a pattern similar to plasma with a rapid secretion of radioactivity into urine which correlates well with the exponential decrease in plasma and urine. The administration of probenecid significantly increases radioactivity due to pipecolic acid in brain, liver, and urine. Formation of α-aminoadipic acid, a known metabolite of pipecolic acid, can be demonstrated in kidney 30 min after intraperitoneal injection. The present data together with results obtained previously with intracarotid injections suggest that pipecolic acid is taken up in the mouse brain from the circulation. Most of the

¹ Present address: Department of Pharmacology, Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-Ku, Hiroshima 734, Japan.
² To whom all correspondence should be addressed.
pipecolic acid taken up is rapidly removed through the circulation and secreted in the urine; however, a small part is retained and probably metabolized by brain and kidney.

INTRODUCTION

Pipecolic acid has recently been demonstrated to be present in the mouse brain (1). We have shown that in the mouse brain the biosynthetic pathway which leads to the piperidine nucleus of pipecolic acid originates from lysine via one of the intermediates of lysine metabolism (2–4). Similarly, pipecolic acid is a major product of lysine metabolism in rat brain (5, 6). A high affinity, temperature, and Na$^{+}$ dependent uptake system has been recently demonstrated in synaptosomes from mouse brain (7), as well as Ca$^{2+}$ dependent, high K$^{+}$ induced release in rat brain slices (8). Plasma/brain ratios of lysine following i.v. injections of labeled lysine demonstrated that in both mouse and rat a blood brain barrier (BBB) for this precursor amino acid is not particularly effective (9, 10). In the same experiments in the rat (10), labeled pipecolic acid was detected in significant amounts within 30 sec following intraventricular injection of lysine, indicating a high rate of formation. By applying a modification of the method described by Oldendorf in the rat (11), we have compared the BUI (Brain Uptake Index) of pipecolic acid in the mouse brain to that of several amino acids and amines (12, 13). This rapid tracer technique demonstrated that an appreciable amount of pipecolic acid can cross the BBB and enter the brain. The BUI of $[^{3}$H]$D,L$-pipecolic acid was found to be 3.39. This places pipecolic acid in the same category as acidic amino acids and amines, i.e., substances with a low transport rate (11, 14). The kinetic analysis suggested two kinds of transport systems (13). These and other results (1, 13) indicate that the entry of pipecolic acid into brain involves more than simple diffusion.

High levels of pipecolic acid in brain, serum, and urine have been associated with severe mental retardation and degeneration of the nervous systems in humans (15, 16). Either an impairment of pipecolic acid synthesis and metabolism in brain or a breakdown of the BBB for this iminoacid could constitute a major defect in this disease. On the other hand, pipecolic acid which is derived from the diet or from synthesis in other organs, such as large intestine, liver, and kidney, could be transported to the brain and accumulated there (1, 2).

It is therefore important to determine the kind of transport mechanism which might be responsible for building up cerebral levels of this substance. A subsequent, but not secondary question, is whether pipecolic