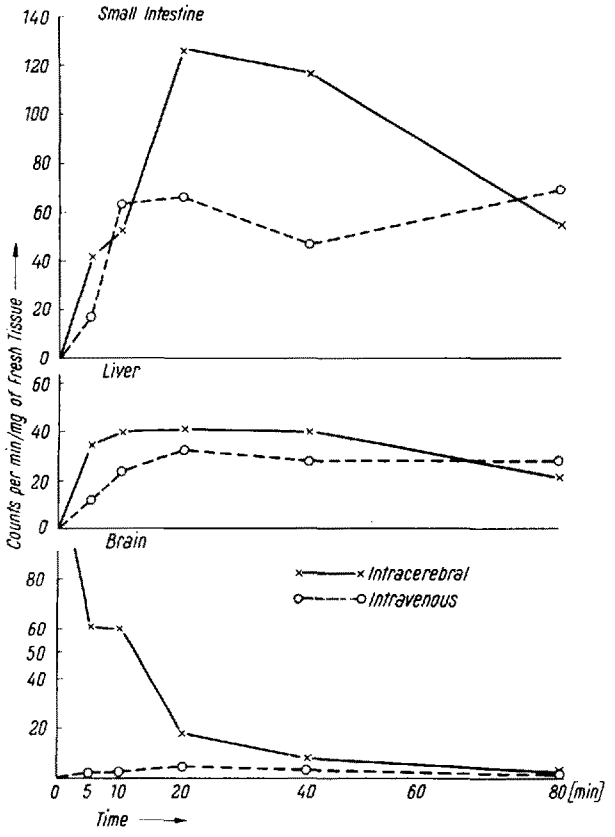
voie de développement, atteignent une plus grande taille. L'auteur suppose que ce phénomène est dû à la prolongation de la durée d'activité de l'hormone somatotrope du foie atteint.

Brain Concentrations of LSD-25 (Delysid) after Intracerebral or Intravenous Administration in Conscious Animals

After intraperitoneal administration of C^{14} labelled LSD to rats, BOYD *et al.*[1] found 48·5–71·2% of the dose in the gastrointestinal tract. LANZ, CERLETTI, and ROTHLIN[2] showed that the drug disappeared rapidly from the blood and concentrated in the liver. The concentration in the brain also decreased rapidly but was independent of the blood level after equilibrium had been established. In the mouse STOLL *et al.*[3] showed that intravenous C^{14}-Delysid underwent chemical alteration and was rapidly excreted via the liver and bile into the small intestine. Similar results were obtained in rats with biliary fistulas. In all cases the concentration of the drug in the brain was extremely small. In view of the profound psychic changes induced by very small doses of Delysid, it is essential to obtain more information to correlate brain concentrations with behavoral changes. We have now undertaken experiments to study the distribution and elimination of LSD in animals, a relatively high brain concentration of LSD being produced by intracerebral injection. We also compared these animals with control animals treated with the drug by the intravenous route. The concentration of the C^{14}-LSD and its metabolites in the brain, liver, and small intestine was followed by activity measurements using the same procedures and counting equipment as previously described by STOLL *et al.*[4].

The C^{14}-Delysid (25 μg, 2·73 $\times$ 10^5 c.p.m. per animal) was injected intracerebrally according to the procedure of HALEY and MCCORMICK[5] or intravenously via the caudal vein of white mice, which were decapitated in series of five after 5, 10, 20, 40 and 80 min. The organs of the same group and series were combined, homogenized with water, and aliquots of the suspension were analyzed after freeze-drying. The results presented graphically in the Figure are based on the mean of two determinations.

Changes in behavior of the mice began immediately after intracerebral injection and 3 min after intravenous injection; after that time the effects were indistinguishable in the two groups. The changes included hyperexcitability, sensitivity to sound and touch, piloerection, and a peculiar muscle twitch in the lumbar area accompanied by alternate stamping of all 4 feet. These symptoms were still present at the end of the observation period when the concentration of the drug in the brain had reached its lowest level, independently of the route of administration. This indicates that the very small amounts of the drug entering the brain after intravenous injection are sufficient to produce similar effects to those caused by the relatively large quantities introduced by intracerebral administration.



Radioactivity of organs after intracerebral and intravenous application of 25 μg C^{14}-Delysid per animal

The most surprising result of the present experiments is, however, the rapidity with which, after intracerebral injection, the drug leaves the brain, appears in the liver, and is excreted into the intestine (Figure). During the first hour of the experiment the concentration in the liver and the small intestine is even greater after intracerebral than after intravenous injection. Although this last finding cannot be completely explained at the present time, the results show very clearly that contrary to experience with other substances, e.g. adrenaline, the blood-brain barrier is only efficient for the inflow of Delysid from blood into the brain but practically nonexistent for the outflow from brain into the blood. A similarly rapid disappearance of LSD from the brain was confirmed in an experiment on 4 cats with FELDBERG-SHERWOOD cannulae[6]. The intraventricular injection of 50 μg/kg (0·1 ml/kg of a solution containing 5·47 $\times$ 10^6 c.p.m./ml) resulted in a brain concentration of only 8–10% of the injected dose when the cats were sacrificed 10 min after injection. At this time the drug was already beginning to concentrate in the bile.

These experiments provide renewed evidence that only very low brain concentrations of Delysid are required to induce prolonged behavioral changes. The extremely rapid removal of LSD from the brain supports the idea that such changes are due rather to a reaction

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[5] T. J. HALEY and W. G. MCCORMICK, Brit. J. Pharmacol. (in press).

[6] W. FELDBERG and S. L. SHERWOOD, J. Physiol. *120*, 3P (1953)

sequence triggered by LSD than to the permanent presence of the drug in the central nervous system.

T. J. HALEY and J. RUTSCHMANN

Research Laboratories, Sandoz Ltd., Basle, Switzerland, January 18, 1957.

Zusammenfassung

Die Radioaktivität in Gehirn, Leber und Dünndarm der Maus nach intravenöser und nach intrazerebraler Injektion von ^{14}C-Lysergsäure-diäthylamid (Delysid) wurde bestimmt. Es ergibt sich, dass die radioaktive Substanz nach intrazerebraler Injektion mindestens ebenso schnell in der Leber erscheint und durch die Galle in den Dünndarm ausgeschieden wird, als das bei intravenöser Anwendung der Fall ist. Da nach intravenöser Injektion des markierten Delysids nur eine minimale Aktivität im Gehirn erreicht wird, kann geschlossen werden, dass die Blut-Liquor-Schranke wohl den Übertritt des Delysids vom Blut ins Gehirn weitgehend hemmt, aber den Austritt der Verbindung aus dem Gehirn nicht behindert.

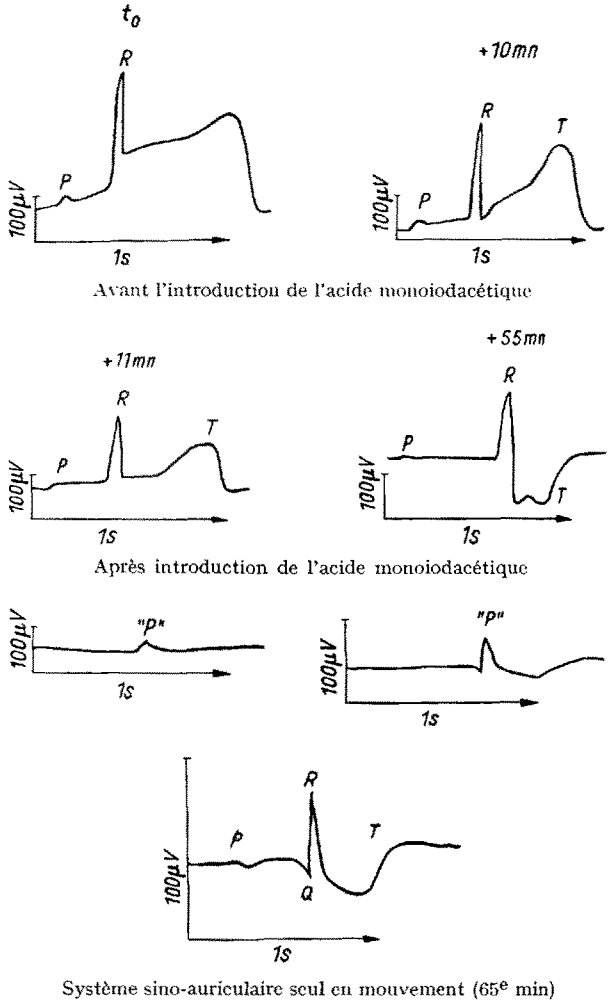
Die schnelle Ausscheidung von ^{14}C-markiertem Delysid aus dem Gehirn nach intraventrikulärer Injektion wurde in Versuchen an der Katze bestätigt.

L'asphyxie, moyen d'analyse de l'électrocardiogramme de grenouille

Dans un précédent travail[1] nous avons montré par voie chirurgicale, que le système sino-auriculaire – voire le sinus veineux seul – de grenouille pouvait livrer un train d'ondes électriques ternaire à sommets PRT. La voie chimique peut être une autre manière d'isoler les éléments d'un même système et peut l'être de façon aussi efficace que la manière chirurgicale. Précisément, avec l'acide monoiodacétique, il est possible de dissocier le fonctionnement auriculaire du fonctionnement ventriculaire du cœur de grenouille. En aérobiose, en solution de Ringer, à 20°C, un cœur subtotal[1] isolé, non perfusé mais soumis à une agitation périodique selon la méthode élaborée[2], montre un train d'ondes électriques ternaire typique. L'adjonction d'une solution de Ringer renfermant de l'acide monoiodacétique de telle sorte que la concentration finale en cet inhibiteur soit approximativement de $0{,}15 \cdot 10^{-3}$ *M*, amène, après 1 h environ, l'arrêt de la contraction ventriculaire tandis que se maintient la contraction sino-auriculaire. Or, après amplification convenable, le tracé électrographique restitue un train d'ondes électriques ternaire à sommets PRT. La Figure ci-contre fait état de ces résultats.

Des faits comparables peuvent être obtenus au moment de l'arrêt ventriculaire avec un cœur subtotal de grenouille, placé en atmosphère d'azote dans du Ringer glucosé à 0,5 g/l.

Le maintien de la seule activité sino-auriculaire nous paraît être la conséquence du métabolisme principalement – si ce n'est exclusivement – glucidique du ventricule[3], le glycogène en étant la source essentielle[4]. D'une part le système sino-auriculaire aurait un métabolisme non-exclusivement glucidique et, d'autre part, par suite de l'épaisseur du ventricule et de la minceur du système sino-auriculaire, l'asphyxie doit se faire sentir plus rapidement dans le ventricule que dans le système sino-



Avant l'introduction de l'acide monoiodacétique

Après introduction de l'acide monoiodacétique

Système sino-auriculaire seul en mouvement (65e min)

auriculaire amenant l'arrêt du ventricule. Dans ces conditions le court-circuitage électrique par le ventricule ne se réalise plus et, seul, le système sino-auriculaire, encore fonctionnel, peut livrer, à l'amplitude près, un train d'ondes complet.

B. RYBAK et J. TRÉPEAU

Faculté des Sciences, Bordeaux, le 14 janvier 1957.

Summary

When the ventricle of the frog heart is stopped in anaerobiosis or in aerobic conditions by means of iodacetic acid, the sino-auricular system alone can give PRT deflections detected by a high electrical amplification.

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