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AMINOPYRIDINES AND SIMILARLY ACTING DRUGS
Effects on Nerves, Muscles and Synapses


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When I suggested to my colleagues William Bowman and Stephen Thesleff that we organize a Symposium dedicated to aminopyridines and related compounds, they were immediately enthusiastic in supporting my proposal. We all three agreed indeed that such derivatives have provided an ever increasing interest in neurophysiology and neuropharmacology in the last twenty five years. Fortunately our project rapidly received support from all of the colleagues we contacted in order to deliver lectures. Many scientists all round the world have published papers using aminopyridines as tools for investigating ionic channel properties and the mechanisms involved in neurotransmission at different levels: neuromuscular junction, as well as central and autonomic synapses. Moreover was it not a wonder to have such a simple chemical with such a powerful activity, therefore so very tempting for all those engaged in structure-activity relationship studies? Some new therapeutic perspectives have also been opened by these derivatives. It seemed therefore useful to have a meeting where workers, old pioneers as well as young researchers, could present their results and discuss all together. The two-and-a-half day Symposium that took place in Paris in July 1981 seems to have achieved this aim. Like all scientific meetings of limited size, it enabled its one hundred participants to have personal contacts and lay fundations for future fruitful collaboration between laboratories. The contributions of participants from 25 countries comprised an up-to-date review of present knowledge and hopefully served to stimulate future research.

The present Proceedings have been organized in eight sections according to the original Scientific Programme. They include the full papers of invited Lectures, Abstracts of oral Communications and Posters presented. The available discussions have been added after the respective scientific sessions. In order to achieve a rapid publication of these Proceedings, the texts have been prepared directly by the authors which are fully responsible for their camera-ready typescripts.

Finally, it is a pleasure to acknowledge my indebtedness to my collaborators Drs. Madeleine Lemeignan and Jordi Molgo for their untiring efforts in preparing the meeting as well as these Proceedings. I wish also to thank the technicians and secretary of my laboratory Mrs. Chantal Angeli, Mrs. Jeanine Josso, Mrs. Nicole Lettérón and Miss Annie Rodallec for their valuable assistance in preparing the meeting and during the scientific sessions.

Let me hope that the reading of these Proceedings will provide the best justification for this Symposium, opening the way to another one in a few years...

Paul Lechat
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The aim of this historical review is to recall briefly the main steps of the pharmacological studies carried out on aminopyridines (AP) and related compounds. Initial works describing a given effect or proposing a mechanism of action or a therapeutic application are cited here as important milestones in our story.

Pyridine was isolated from coal tar by Anderson in 1846, and picoline (methylpyridine) appeared to be the first heterocyclic compound obtained by synthesis through the work of Klaus in 1862.

It is interesting to note that the first pharmacological investigation using pyridine concerned its action on neuromuscular transmission. The results were presented in 1883 to the Société de Biologie by Bochefontaine, who worked in Vulpian's laboratory in the Paris School of Medicine, where my own laboratory is now located. At that time Bochefontaine reported the depressive action of pyridine on neuromuscular transmission, just the opposite to what we know to be the effect of aminopyridines today.

The three isomeric aminopyridines were obtained in 1894 by Meyer, who used the Hofmann procedure (treatment of the amides of pyridine monocarboxylic acids by alkaline hypobromites). In 1915 Tchitchibabine obtained 2-AP by heating pyridine with sodamide. The six possible diaminopyridines were synthesised later.

In 1925 Mr. Dohrn from Charlottenburg wrote a short paper entitled "Pharmakologie einiger Pyridinderivate" in the famous German Journal "Naunyn Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie". In a few lines, the author described the following effects of amino-2 pyridine:

- convulsions in frogs, mice and rabbits, which were not suppressed by decapitation, disappeared immediately after the spinal cord was destroyed, although fascicular tremors continued to persist. These tremors did not cease after cutting of the innervating nerves, but disappeared after their degeneration.
- stimulation of isolated gastrocnemius, as with guanidine.
- strong rise in blood pressure.
- strong elevation of isolated gut tonus.

The introduction of a second amino group leading to 2,6-diaminopyridine did not modify the activity, but an acetyl group reduced the toxicity.

This was indeed a remarkable achievement to which there is little to add today.

Our present knowledge of the mechanism of AP action is much deeper, but it was Dr. Dohrn who described concisely and with great precision the main pharmacological properties of 2-AP, and that was 56 years ago.

In order to be more clear, I wish to go through the sequence of discoveries by examining one after the other the different actions of AP on the organism.