Myoclonia in *Papio papio*: Are They All "Epileptic"?

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INTRODUCTION

At the beginning of the 1970s, electrical stimulation of the cerebellum was proposed to act against cerebral hyperexcitability and to block the oncoming of epileptic seizures in both humans and animals. Experiments carried out in Mexico (Fernandez-Guardiola et al, 1976) and American studies (Myers et al, 1974; 1975) provided hope that electrical stimulation of the cerebellar cortex, via subpial electrodes placed chronically at the level of the vermis, could be an effective treatment for certain intractable epilepsies.

With Simon Brailowsky spending his first period in the laboratory, it seemed interesting to us to consider the possibility, not of stimulating the cerebellum but rather of investigating the influences of cerebellar lesions on myoclonia or seizures that are induced by intermittent light stimulation (ILS) in the baboon *Papio papio* (Brailowsky et al.,1975; 1978). These baboons were already known (Killam et al 1966; Balzamo et al, 1975) to present two types of myoclonia: (1) the myoclonia to ILS, which were well studied at this time and (2) the myoclonia to contact or surprise (action and attention myoclonia) just mentioned above. Brailowsky was the first to really study myoclonia. The data that he obtained at that time has given rise today, 20 years later, to unresolved and interesting scientific problems.

MYOCLONIA "A"

Papio papio photosensitive epilepsy is very frequent (60%) in animals captured in Casamance, Senegal. When animals are submitted to ILS, this condition is characterized by the appearance of reflex paroxysmal electroencephalographic (EEG) discharges that are always bilateral and synchronous and occupy large cortical territories, particularly the frontorolandic areas (Killam et al, 1966; 1967; Fischer-Williams et al., 1968; Ménini et al, 1994). The paroxysmal discharges are associated with clinical paroxysmal manifestations: bilateral and synchronous myoclonia, which begin with myoclonia of the eyelids, spreading to involve the face, the neck, the limb extremities, and then the rest of the body (Killam et al., 1967). The myoclonia can be followed, after ILS cessation, by self-sustained bilateral myoclonia or generalized convulsive seizures, analogous to Grand Mal seizures of human patients. Such myoclonia were later called "myoclonia A" (Valin et al, 1983).

The effects of many anti-epileptic drugs were tested in these myoclonia A (see Meldrum et al, 1978; Naquet & Meldrum, 1985): the more effective medications are those that are known to act in "generalized" epilepsy in man. One may cite, for example, the benzodiazepines and the antagonists of excitatory amino acids (Chapman et al, 1994). In animals, sodium valproate was also very effective, but at doses higher than those used in humans (Naquet & Meldrum, 1985). As a consequence, myoclonia A was considered for years as an excellent model for testing the effects of many drugs that were suspected to have the power to act on the epileptic susceptibility of a subject.

MYOCLONIA "B"

This kind of seizure was first mentioned and described by Serbanescu (personal communication) in young, non-photosensitive baboons, *P.*

papio, during an exploratory mission in Senegal in 1968. The condition was further described by Brailowsky et al. (1978) and later called myoclonia "B" (Valin et al, 1983). Myoclonia "B" can be either associated or not associated with myoclonia "A".

Myoclonia "B" are bilateral, "massive", spontaneous, and involuntary and first affect the muscles of the neck and trunk, especially those of the shoulder; the muscles of the face and limbs are not affected or only secondarily involved. These myoclonia are never preceded nor accompanied by a paroxysmal EEG discharge in the frontorolandic region, but rather are followed by a normal evoked potential around the vertex. Myoclonia "B" are never followed by self-sustained EEG paroxysmal discharges and Grand Mal seizure. Myoclonia "B" appear in isolation or in irregular bursts when the animals are agitated. Active movements of *P. papio*, startle, or proprioceptive stimulation facilitate the appearance of myoclonia "B".

Myoclonia "B" are increased by the following different, well-described conditions:

1. *The facilitator effect of vermis ablation (Brailowsky et al, 1978)*: The ablation of the vermis was performed to determine whether such surgical intervention will be able to facilitate, under ILS, the appearance of myoclonia A and Grand Mal seizures in photosensitive *P. papio.* The results demonstrated that the vermisectomy does not modify, at any time (days and weeks after surgery), the level of photosensitivity of the baboons.
   a) Baboons, either photosensitive or not, showed, after vermisectomy, a cerebellar syndrome with atonia and postural disturbances, which disappeared progressively within 2 to 3 weeks.
   b) Myoclonia "B" are seen at the time of recuperation of the cerebellar syndrome. The myoclonia appear in all *P. papio* baboons, presenting them or not before surgery. After vermisectomy, myoclonia are very frequent and tend to occur in long bursts.

   The data showed that:
   a) myoclonia "A" and "B" respond in a different manner to vermisectomy, with myoclonia "A" being not at all affected and myoclonia "B" being very enhanced,
   b) photosensitive baboons with vermal ablation show two types of myoclonia, "epileptic" and "non-epileptic", clearly distinguishable by their clinical and electrographic symptoms and mode of onset, yet both types can be associated in the same animal.

   Researchers concluded at that time that myoclonia "B" seem to originate in the brain stem and appear similar to a certain type of action myoclonia, different from those described in humans (see Hallett et al., 1977).

   Later, Ménini et al (1994) demonstrated that myoclonia "A" and "B" can co-exist, in the same non-operated *P. papio*, whether the animals are photosensitive or not. In other *P. papio*, neither type of myoclonia exists. Statistical analysis of the data obtained in 106 baboons for this purpose showed that myoclonia "A" and "B" are independent of each other.
2. *Facilitator effect of benzodiazepines (Valin et al, 1981):* A few years later, testing the anti-convulsant effects of lorazepam on ILS-induced myoclonia "A", Valin and colleagues (1981) observed that this drug blocked myoclonia "A" and facilitated the occurrence of myoclonia "B". Interestingly, these two effects have different temporal evolutions. After the intravenous injection of lorazepam and depending on the dose, the effect against myoclonia "A" occurs in a few seconds, reaching a maximum at 2 min and lasting for about 1 h. The myoclonia "B" occur later, reaching a maximum at 30 to 40 min and lasting, also depending on the dose, for 3 to 5 h, such that a period exists during which both myoclonia can be induced alternatively.

   Myoclonia "B" are similarly induced or facilitated when lorazepam is administered to non-photosensitive baboons. All benzodiazepines tested act in the same way. The duration of the period preceding their appearance is variable, as is the duration of

their efficacy. In each case the effect on "B" appears later and is much larger than that on "A".

Pharmacological studies have demonstrated that the cholinergic system is involved in the generation of myoclonia "B" and that the facilitating action of benzodiazepines appears, in fact, to result from an indirect action of benzodiazepines on the cholinergic system (Rektor et al, 1984; 1986; 1990). These myoclonia "B" may be induced by atropine, an anticholinergic drug, and are blocked by physostigmine, a substance that increases the cerebral level of acetylcholine. Conversely, the cholinergic system does not act on myoclonia "A".

DISCUSSION

A. Following the results obtained in *P. papio,* myoclonia "A" and "B" were characterized and differentiated: No one denies that myoclonia "A" are "epileptic" because they are always preceded by EEG paroxysmal discharges. Myoclonia "A" are corticofrontal in origin.

By contrast, myoclonia "B" have been considered as "non-epileptic" because they are neither preceded by nor accompanied by EEG paroxysmal discharges. Taking into account these results, Menini & Naquet (1986) proposed that such myoclonia originate in the low brain stem, particularly in the reticular formation (Rektor et al., 1993) and that they may be the consequence of putting into play short circuits that are induced by somatosensory influences and involving only low brain stem and cerebellar circuits.

Such differences between them is perhaps too schematic, and Naquet and Batini (1999) recently suggested that

> "*. . . due to the fact that it was impossible to produce myoclonus of the eyelids by electrical stimulation of the frontorolandic area where the spikes and waves (EEG paroxysmal discharges) are induced by ILS, the question of the origin of these myoclonia "A" is still under discussion; their progression from eyelids to the face, or to other muscles of the body, resembles to an extension around the nuclei of the brain stem. Knowing that they never appear without being preceded by spikes and waves in the frontorolandic area, it was proposed that they are the consequence of put into play of corticothalamic circuits under ILS and secondary circuits including the high part of the brain stem.*"

However this may be, ILS and somatosensorial stimulation bring into play different circuits and provoke myoclonia in *P. papio,* which manifest or react differently from a clinical, EEG, and pharmacological point of view. The question remains to define the "epileptic" or "non-epileptic" origin of each type of myoclonia. That they may coexist in the same animal does not simplify the answer.

B. The study in *P. papio* cannot go further in the differentiation of the origin of myoclonia "A" and "B". Experiments that were recently carried out on the epileptic Fayoumi chicken (*Fepi*) permits further differentiation. The Fayoumi chicken, described by Crawford et al (1970), carries an autosomal recessive mutation and presents continuous EEG interictal paroxysmal manifestations, exhibiting a form of "reflex epilepsy' that is induced by ILS or sound stimulation. This "reflex epilepsy" reacts to anticonvulsant drugs, analogous to those acting in *P. papio* and humans (Johnson & Davis, 1983). Under ILS, *Fepi* present myoclonia of the neck, rapidly followed by generalized myoclonia, running, and seizures consisting of generalized convulsions. During this seizure, the only EEG symptomatology observed is a desynchronization.

By using the brain chimera technique (see Le Douarin, 1993), it was demonstrated that in a normal embryonic strain: (Batini et al 1996)

a) grafting embryonic *Fepi* from the prosencephalon (from which the "wulst" originate) to the mesencephalon reproduces the complete phenotype of the *Fepi.*
b) grafting only embryonic *Fepi* prosencephalon results in an interictal EEG analogous to that of the *Fepi.* ILS induces desynchronization, but does not induce myoclonia or seizures.

c) grafting only embryonic *Fepi* mesencephalon results in a normal interictal EEG. ILS induces myoclonia of the neck after each stimulus; myoclonia are never followed by a seizure.

One may conclude that myoclonia induced by ILS in the chicken start in the brain stem and are not associated with any EEG paroxysmal discharge. The mesencephalon contains the generator of myoclonia, with the exception of the abnormal EEG, which is transmitted exclusively by telencephalic grafts. If we take into consideration the interictal EEG, the *Fepi* is predisposed to "classical epilepsy"; but the observation that myoclonia and seizures induced by ILS are not accompanied by EEG paroxysmal discharge again raises the problem of their "epileptic" or 'non-epileptic" origin .

C. Are the myoclonia of the brain stem epileptic in origin? A comparison between the symptomatology of the myoclonia "B" of *P. papio* and the myoclonia induced by ILS in mesencephalic *Fepi* chimera confirms that the brain stem plays a crucial role in myoclonia generation. The problem of terminology in the appellation of the myoclonia of brain stem as "epileptic" in origin is more difficult because they are not accompanied by any EEG paroxysmal discharge under sensory stimulations (somatosensory in *P. papio*, ILS in *Fepi*):

1) the *Fepi* chicken, which like audiogenic rodents (also presenting seizures without EEG paroxysmal discharge), reacts to all antiepileptic drugs that are effective in man and in *P. papio,* is considered a very important model for testing such anti-epileptic drugs. The seizures of both models are called, without restriction, by pharmacologists "reflex epilepsy" (see Chapman & Meldrum, 1993; Job et al, 1994; Johnson & Davis, 1983).
2) myoclonia "B" of *P. papio* is less simple:
   a) myoclonia "A" and "B" may be found in the same animal, without any drug or surgery, and no one denies that myoclonia "A" are "epileptic".
   b) myoclonia "A" and "B" do not react in the same manner to anticonvulsant or antiepileptic drugs.

This could suggest that myoclonia "A" and "B" are not of the same origin, a reason why myoclonia "B" have been considered "non-epileptic". But it seems difficult to admit that in the same animal predisposed to epilepsy a myoclonia may be called "epileptic" or "not epileptic" depending on circuits put into play by two different sensori stimuli. The difference seems to be not between "epileptic" or "non-epileptic", but rather between corticothalamic circuits or brain stem circuits.

One may transfer this concept to certain clinical paroxysmal manifestations in humans. Because certain myoclonia or seizures (Startle disease, Paroxysmal Kinesigenic Choreoathetosis) are not accompanied by any EEG paroxysmal discharge, they are not considered "epileptic" and are called "Movement disorders" (see Naquet & Batini, 1999); nevertheless, such conditions react well to antiepileptic drugs, and in the families, "classic" epileptic seizures exist.

For all these reasons, Naquet and Batini (1999) proposed calling all sensory-induced paroxysmal manifestations, from chicken to human, "reflex epilepsy". This classification is based on the statement that

> *"one does not know, at this time, why a normal sensori brain stem reflex is transformed, in predisposed animal, in a myoclonia or in a generalized seizure, and why such paroxysmal 'clinical' manifestations do not have a characteristic 'epileptic' EEG expression when they stay localized in the brain stem. One may hope thath molecular genetics will bring some data which will permit going further in their comprehension and will help to propose a better definition of genetic reflex myoclonia and particularly for the one of the* Papio papio. *"*

Such a position was intended to be provocative. It will clash head-on with a good number of

established ideas, but it seems necessary at one moment to try to go further in the definition of "what is epilepsy" or "what is not epilepsy". The implication of the cortex is or is not necessary to call a paroxysmal clinical manifestation "epileptic" in man? The existence of an EEG paroxysmal discharge accompanying the paroxysmal clinical manifestation is or is not necessary to call it "epileptic"? An EEG with paroxysmal discharges recorded in a subject presenting no clinical "paroxysmal manifestation" is or is not sufficient to consider him as epileptic? That the seizures of the genetic "epilepsy" of chickens and rodents have no paroxysmal EEG expression is or is not sufficient to consider them as "epileptic"?

On the basis of the importance of the cortex in epilepsies and on the classical EEG expression of epileptic manifestations, one of the present authors (see Naquet & Wada, 1986) considered, for several years, that the audiogenic epilepsy of rodents, and the myoclonia "B" of *P. papio* were not "epileptic" (Menini & Naquet, 1985). The results obtained with rodents (Le Gall La Salle & Naquet,1990) and with the Fayoumi chicken (Batini et al., 1996), despite their differences of corticalisation with primates, forced us to think anew about "what is epilepsy". The result of this reflection is that myoclonia "B" must be considered as "epileptic". This point of view cannot be definitive at the present time. The aim of this approach is to raise questions, to provoke discussions, and eventually, to inspire new experiments. Seeing how far this purpose will be followed will be interesting.

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