**Nervous excitability study**

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Based on conduction studies and electromyography, electrodiagnosis is an essential technique for characterizing peripheral neuropathies and quantifying their degree of damage. Axonal excitability study does not participate routinely to the diagnosis of peripheral neuropathies. Yet electrodiagnosis history, early in the 20th century, began by neuronal excitability studies. Weiss and Lapicque described the first parameters to quantify nervous excitability, **chronaxie and rheobase** (Weiss, 1901; Lapicque and Lapicque, 1903). The rheobase is the estimated threshold current for a stimulus of infinitely long duration. The chronaxie is the minimum stimulus duration for a current twice rheobase to stimulate a muscle.

Later, studies on isolated nerve fibers measured the **recovery cycle** with a sequence of refractoriness (absolute refractory period and relative refractory period), supernormal excitability and subnormal excitability (Bergmans, 1970). The recovery of excitability after a single supramaximal conditioning stimulus can assess these parameters using paired pulse with varying inter-stimulus interval typically between 2 and 200 ms. The major determinant of the recovery from refractoriness is the recovery of Na+ channels from inactivation. Supernormal period comes from ‘‘back-flow” of current from the internodal membrane. The amount of current stored in the internodal membrane varies with membrane potential as paranodal fast K+ channels are either opened or closed. Late subnormal period is due to slow K+ channels. This technique allows not only to study Na+ and K+ channels but also provides information about the membrane potential. Indeed, when the membrane is depolarized, supernormal period decreases and refractory period increases. When the membrane is hyperpolarized, changes are in opposite direction.

Another approach to assess nerve excitability is the **stimulus–response curve** (Brismar, 1985; Boërio et al., 2008). This method establishes the nerve threshold range curve from the relation between compound muscle action potential (CMAP) size and strength of the stimulus to the nerve. Cappelen-Smith et al. (2001) used these curves to compare healthy subjects and patients with CIDP. They demonstrated that thresholds of intensity are increased in CIDP especially near the maximal CMAP size. From this curve, we developed a novel and practical tool to assess peripheral motor axon excitability called the “iMAX” which correspond to the minimal current intensity required to obtain a maximal CMAP size (Tyberghein, 2022). This technique can highlight motor axon excitability disorders and could be useful to distinguish a healthy population from a population affected by a demyelinating neuropathy.

In recent years, most of publications about peripheral nerve excitability come from Bostock and Kiernan, pioneers of the so- called **threshold tracking and threshold electrotonus** (Bostock et al., 1998; Kiernan et al., 2020). The basic principle of threshold tracking techniques is to measure the strength of the stimulus required to produce a CMAP of a specified size (near 40% of the maximal CMAP size) termed the ‘‘threshold” in different experimental conditions. This method allows to indirectly examine membrane potential changes that occur during long (100–200 ms) subthreshold current pulses (threshold electrotonus), demonstrating properties of the internodal membrane.

Axonal excitability studies provide information about ion channel function and surrogate markers of axonal membrane potential in vivo in human axons. These techniques are promising to get a better understanding of the physiopathology of peripheral neuropathies.

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