Brain Research Bulletin 103 (2014) 2–10

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

# Dendritic integration in pyramidal neurons during network activity and disease

Lucy M. Palmer*

*Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria 3100, Australia*

ARTICLE INFO

*Article history:*
Received 12 July 2013
Received in revised form
18 September 2013
Accepted 19 September 2013
Available online 2 October 2013

*Keywords:*
Dendrites
Integration
Disease
Pyramidal neurons

ABSTRACT

Neurons have intricate dendritic morphologies which come in an array of shapes and sizes. Not only do they give neurons their unique appearance, but dendrites also endow neurons with the ability to receive and transform synaptic inputs. We now have a wealth of information about the functioning of dendrites which suggests that the integration of synaptic inputs is highly dependent on both dendritic properties and neuronal input patterns. It has been shown that dendrites can perform non-linear processing, actively transforming synaptic input into $Na^+$ spikes, $Ca^{2+}$ plateau spikes and NMDA spikes. These membrane non-linearities can have a large impact on the neuronal output and have been shown to be regulated by numerous factors including synaptic inhibition. Many neuropathological diseases involve changes in how dendrites receive and package synaptic input by altering dendritic spine characteristics, ion channel expression and the inhibitory control of dendrites. This review focuses on the role of dendrites in integrating and transforming input and what goes wrong in the case of neuropathological diseases.

This article is part of a Special Issue entitled 'Dendrites and Disease'.



**Contents**



## 1. Introduction

The task of understanding how neurons translate input to output is central to explaining brain function. Since the majority of inputs arrive at the dendrites of neurons, it is critical to understand the processing performed by dendritic trees which leads to action potential output. This can be achieved by looking at different levels of detail in a single neuron, from the activity in a dendritic spine to the functioning of an entire dendritic arbor (Fig. 1). Historically, even though dendrites of various neurons were shown to have active membranes (Llinas et al., 1968; Kuno and Llinas, 1970), dendrites were often treated as non-active structures that collected synaptic signals and relayed them passively to the axonal action potential initiation zone. However, it is now well established that dendrites have active conductances which support various processes and non-linear

* Tel.: +61 9035 3628; fax: +61 (3) 9035 3107.
*E-mail address:* lucy.palmer@florey.edu.au

0361-9230/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brainresbull.2013.09.010

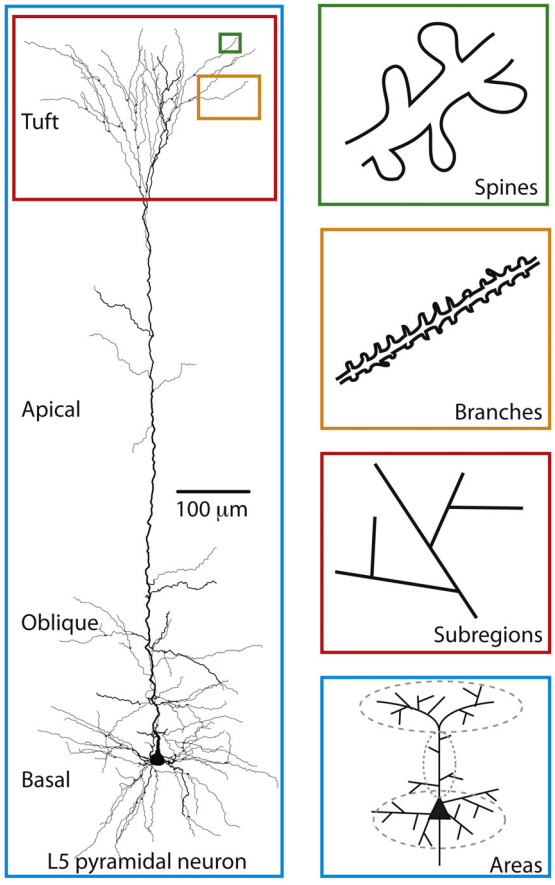


**Fig. 1.** Levels of dendritic integration. Pyramidal neurons have different dendritic areas (Basal, Oblique, Apical, Tuft) and can integrate information at the level of the spine, single dendritic branch, subregion of dendritic branches or entire dendritic area.

input transformations (for a review, see Johnston and Narayanan, 2008).

Dendrites (and axons) were first described by Deiters (1865). Since then, dendrites have been further characterized according to their morphological characteristics (Fig. 1a). The different pyramidal neuron dendritic areas (basal, oblique, apical, tuft) are often located in spatially distinct brain layers and they therefore receive different input streams of information. For example, the basal dendrites of cortical pyramidal neurons receive the majority of synaptic inputs (Larkman, 1991) which largely carry feed forward information (Felleman and Van Essen, 1991). Conversely, the tuft dendrites receive long-range feedback input from other cortical areas and the thalamus including the posterior medial nucleus (POm) of the thalamus (Rubio-Garrido et al., 2009), the secondary somatosensory cortex (Cauller et al., 1998) and parahippocampal structures (Witter and Groenewegen, 1986). How, and even whether, these different pathways are integrated at the cellular level by dendritic processes has been the source of debate for decades.

Despite their central role in cellular processing of information, our understanding of dendritic functioning has lagged behind other fields of neuroscience research. This is largely due to the difficulty in recording from the very thin dendritic structures, which are often less than 1 μm in diameter. However, recent advances in imaging techniques have now opened this field of research. This review will examine how dendrites integrate and transform synaptic input and how this process is affected during neurological diseases. Firstly, the different levels of dendritic integration and the resulting linear or non-linear processing will be discussed with the use of both in vitro and in vivo examples. Alterations in dendritic integration during different neuropathological diseases will then be explored, including the influence of changes in dendritic spine morphology and function, ion channel phosphorylation and expression and dendritic inhibition. Lastly, the role of the prefrontal cortex in disease will be briefly discussed. This is not designed to be an exhaustive review of all the changes that occur in neurons during neuropathological diseases, but highlights a few of the reported abnormalities that have drastic effects on dendritic integrative properties. Since much is known about the computation and integrative properties of pyramidal neuron dendrites, namely cortical and hippocampal neurons, this review focuses mainly on these cell types.

## 2. Dendritic integration

In seminal work over half a century ago, Rall described the electrical properties of dendrites and showed that passive dendritic filtering properties prolong the time window for synaptic summation of distal inputs (Rall, 1967; Rall et al., 1967; Rall and Rinzel, 1973). Rall's computational theories predicted that the dendritic site of synaptic input could greatly influence the integrative properties of dendrites. Although the dendrites of neurons have subsequentially been shown not to be passive, Rall's theoretical work still serves as the fundamental framework for understanding dendrites from a biophysical perspective. In particular, compartmental models based on Rall's ideas are still the only realistic way of examining the summation of synaptic input in detail and thereby determining the input/output relationship of a neuron. Nevertheless, models can only be as good as the data they are based on and it is therefore crucial to investigate dendritic properties in relation to realistic input scenarios. Experimental examples have been shown for the three different types of dendritic integration as outlined below.

### 2.1. Sublinear input summation

Conductance based models predict that synaptic input which occurs within close spatial proximity on a dendritic branch will sum sublinearly due to decreases in driving force as the membrane potential nears the reversal potential. Indeed, sublinear integration was reported in cortical layer 2/3 pyramidal neurons (Tamas et al., 2002) and layer 5 pyramidal neurons (Polsky et al., 2004) when large-amplitude convergent input occurred in close spatial proximity in vitro. Sublinear integration has also been reported in the visual cortex in vivo (Fig. 2a). In a study by Longordo et al. (2013), the integration of inputs during binocular stimulation in layer 2/3 pyramidal neurons of the primary visual cortex was reported to be sublinear and the greatest non-linearity occurred at the preferred visual stimulus orientation (when the inputs from the two eyes were large; >15 mV). This non-linear integration was shown to be extremely important in the visually-evoked neuronal response, linearizing action potential output and increasing orientation selectivity in binocular pyramidal neurons. Overall, it appears as though sublinear integration may serve an important role in dampening the impact of synaptic input by reducing the input/output relationship for specific patterns of incoming information.

### 2.2. Linear input summation

Spatially distributed synaptic input (i.e. input that occurs on different dendritic branches) acts independently and therefore integrates linearly (Mel, 1993; Poirazi et al., 2003; Polsky et al., 2004; Losonczy and Magee, 2006). Indeed, subthreshold synaptic input has been shown to be widely distributed throughout the dendritic tree (Jia et al., 2010; Chen et al., 2011b; Hill et al., 2013, although see Bollmann and Engert, 2009). Conversely, spatially clustered synaptic input on a single dendritic branch can also sum linearly