

When taken together, these facts suggest that orexin receptor activity is required to maintain a wakeful state and that cessation of orexin receptor activity promotes sleep. The data also suggest that targeting this receptor with an antagonist would promote normal sleep rather than a global suppression of CNS activity (sedation). These observations do not, however, fully validate this approach. In order to accomplish this, it would be necessary to identify selective orexin receptor antagonists and, more importantly, develop an animal model capable of differentiating between normal sleep and sedation. The key to developing an appropriate animal model was the understanding that brain wave activity, eye movement, and skeletal muscle activity could be used as physiological biomarkers. Changes in each of these biological functions can be monitored using an electroencephalogram, an electrooculogram, and an electromyogram respectively (collectively referred to as polysomnography).<sup>61</sup> Normal sleep and global suppression of CNS activity produce significantly different results in these assays, providing a means for determining the impact of a candidate compound.

In the development of Belsomra<sup>®</sup> (Suvorexant), rats with implanted telemetry equipment designed to record electrocorticogram (an intracranial version of an electroencephalogram) and electromyogram signals were monitored to determine the amount of time each animal spent in the various stages of the sleep/wake cycle in the presence and absence of candidate compounds. A 30 mg/kg oral dose of Belsomra<sup>®</sup> (Suvorexant) produced a significant increase in both REM and delta stage sleep. Decreased wake time was also observed, and importantly, sleep architecture was consistent with normal sleep and rather than global sedation of CNS activity. Receptor occupancy measurements provided further confirmation that changes in sleep architecture were associated with a high level of drug/orexin receptor interaction.<sup>62</sup> Similar results were obtained with Belsomra<sup>®</sup> (Suvorexant) in dogs (1 and 3 mg/kg) and rhesus monkeys (10 mg/kg), highlighting the cross-species consistency of the sleep/wake cycle and the utility of these biomarkers.<sup>63</sup> These same biomarkers were effectively employed in human clinical trials using polysomnography to demonstrate the clinical efficacy of Belsomra<sup>®</sup> (Suvorexant) for the treatment of insomnia. Belsomra<sup>®</sup> (Suvorexant) was approved by the FDA for the treatment of insomnia in August 2014.

## FDG PET Imaging Agent

2-deoxy-2-(<sup>18</sup>F)fluoro-D-glucose (FDG, [Figure 10.3\(b\)](#)) was one of the first radioligands developed for PET imaging.<sup>64</sup> It was originally designed as a replacement for 2-deoxy-D-[<sup>14</sup>C]glucose, a radioligand capable of imaging glycolysis via autoradiography, which requires the animal to