

**COMMENTARY ON: Modulation of synaptic inputs in magnocellular neurones in a rat model of cancer cachexia. Yokoyama T, Terawaki K, Minami K, Miyano K, Nonaka M, Uzu M, Kashiwase Y, Yanagihara K, Ueta Y, Uezono Y. *J NEUROENDOCRINOL* 2018;30: e12630**

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Cancer cachexia describes a wasting syndrome associated with chronic inflammatory conditions during cancer<sup>1</sup> and leads to death in almost a quarter of all patients.<sup>2</sup> It is a multifactorial condition, thus multiple factors may contribute to its development and progression.<sup>3</sup> For example, cancer cachexia progresses at different rates depending on cancer type.<sup>4</sup> Individuals are at a higher risk for cancer cachexia if diagnosed with gastric or pancreatic cancer due to rapid weight loss; conversely, individuals with breast cancer are less likely to develop cancer cachexia.<sup>5</sup> Hallmarks of cachexia include hypophagia and loss of skeletal muscle and body fat, culminating in severe weight loss. These effects typically stem from hormonal imbalances and are thus treated as a metabolic disorder.<sup>3,6</sup> However, it is also known that water intake is positively correlated with food intake.<sup>7</sup> This study by Yokoyama et al found that there was a reduction in water intake with the development of cancer cachexia.<sup>8</sup> These findings suggest that the neurocircuitry underlying fluid balance may contribute to the progression of cancer cachexia.

Yokoyama et al examined the regulation of fluid balance through the neurocircuitry underlying the release of vasopressin,<sup>8</sup> an antidiuretic hormone regulating peripheral osmotic homeostasis.<sup>9</sup> Vasopressin is secreted from magnocellular neurons (MNC) in the supraoptic nucleus of the hypothalamus (SON). When secreted, vasopressin is stored in the pituitary gland and released onto the kidneys to promote fluid retention, as well as increase atrial blood pressure during irregular osmotic conditions.<sup>9</sup> Two factors that regulate vasopressin release are angiotensin II and hyperosmotic stimulation.<sup>10</sup> When blood volume decreases, neurons in the subfornical organ release angiotensin II to stimulate vasopressin release from the SON.<sup>11</sup> Likewise, hyperosmotic conditions also stimulate osmosensory neurons in the subfornical organ and organum vasculosum lamina terminalis to promote vasopressin release.<sup>12</sup> Both angiotensin II<sup>13</sup> and hyperosmotic stimulation<sup>14</sup> increases excitatory glutamatergic input of MNC SON neurons.

Yokoyama et al produced a rat model of cancer cachexia by harvesting human stomach cancer cells<sup>15</sup> and implanting them in Wistar rats to generate stomach tumors.<sup>8</sup> Cachexic rats consumed less food and water and weighed 30% less than healthy age-matched, vehicle-treated control rats. In order to analyze the neurocircuitry underlying fluid balance, Yokoyama et al performed *ex vivo* whole-cell patch clamp recordings from MNC SON neurons and recorded excitatory inputs at SON MNCs in healthy and cachexic rats. They found that angiotensin II and hyperosmotic stimulation, which was pharmacologically-induced by mannitol, increased miniature excitatory

postsynaptic current events at healthy SON MNCs. Interestingly, this stimulatory presynaptic effect of angiotensin II<sup>13</sup> and hyperosmotic stimulation<sup>14</sup> was abolished in tumour-bearing cachexic rats.<sup>8</sup> This indicated that with the development of cancer cachexia, glutamatergic afferents in the SON are less responsive to peripheral osmotic changes, potentially resulting in reduced vasopressin release and water intake.

Current literature on cancer cachexia emphasizes weight loss and hypophagia, with little focus on the role of fluid balance. Therefore, not much is known or understood about fluid balance and how it may mediate the progression of cachexia. Yokoyama et al demonstrated that the neural circuitry underlying fluid balance is compromised in cachexia, which may reduce water intake in afflicted rats. Moreover, as most studies on cachexia focus on food intake and body weight, this study by Yokoyama and colleagues represents a novel and alternative model to study this condition. They provide evidence that water intake and fluid imbalance are valid measures of cachexic symptoms. The fact that cachexia targets synaptic inputs to the SON gives rise to the possibility that additional nodes, such as at the subfornical organ and organum vasculosum lamina terminalis, should be considered in the development of cancer cachexia.

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