Interestingly, neuronal SGK1 may be protective against ischemic ical functions such as fear retention and learning and memory. Recent studies have revealed a contribution of SGK1 to physiolog Mechanism underlying the significance of SGKs: SGK1 encodes a serine/threonine kinase that regulates the function of many pro Mechanism underlying the significance of SGKs: SGK1 encodes a serine/threonine kinase that regulates the function of many pro Possible divergence of serum- and glucocorticoid-inducible kinase function in ischemic brain injury: As recent medical progress decreases the incidence of certain diseases, ischemic brain injury remains one of the major dis brain injury while endothelial SGK1 in the brain microvascu-ature appears to exacerbate outcome after stroke (Zhang et al., 2014, 2015). Thus, as SGK1 activity appears to work in both a beneficial and detrimental manner against ischemic brain injury, and at least partly in a distribution-dependent manner, whether SGK1 should be used as a therapeutic target for specific drugs is uncertain. Furthermore, SGK1 is part of the SGK family that also contains SGK2 and SGK3, with all three family members reported to be expressed in the brain, although their detailed tissue distri-Possible divergence of serum- and glucocorticoid-inducible kinase function in ischemic brain injury: As recent medical progress decreases the incidence of certain diseases, ischemic brain injury remains one of the major dis
inhibitors for each SGK isoform might also help more profound understanding of new therapeutic drugs not only for ischemic brain injury but also for non-invasive administration. It is worth investigating the further significances of these targets for future application.

Figure 1 Scheme of potential interpretation of serum- and glucocorticoid-inducible kinase (SGK) action in ischemic brain injury. According to the literature discussed, an integrative role of SGKs in ischemic brain injury may be beneficial (blue) or detrimental (orange). Consequently, we propose two potential mechanisms: (1) deleterious action of SGK2/3 in neurons; and/or (2) harmful operation of SGKs (including SGK1) in non-neuronal cells (see main text). While current reagents may become potential candidates, a comprehensive understanding of the underlying mechanism and consecutive development of drug(s) for specific SGK isoforms may shed light for greater therapeutic application. BBB: Blood-brain barrier; NMDA-Rs: N-methyl-D-aspartate receptors; PKB: protein kinase B; ZO-1: zonula occludens-1.

their study suggested that SGK1 overexpression activates Akt/protein kinase B (PKB) signaling, which may be a considerable factor regarding anti-apoptotic outcome, as this signaling pathway is regarded to be pro-survival, although at this point it is not clear how SGK1 increases Akt/PKB phosphorylation. Also, Zhang et al. (2014) focused on SGK1, while all SGK subunits were treated in our study. If both findings are taken together, while ignoring the disagreement between conditions (such as species and MCAO duration), there may be two considerable possibilities for the underlying mechanism (Figure 1). First, SGK1 is protective, while other SGKs such as SGK2 and SGK3 may be apoptotic in neurons. Indeed, activity of GluR1-containing glutamate receptor is enhanced by SGK2 and SGK3 and not by SGK1 (Lang et al., 2006), which may lead to an SGK2/3-dependent cytotoxic effect. In line with the contribution of SGKs other than SGK1, a dominant presence of SGK1.1 is also detected in the brain (Artega et al., 2008). The impact of SGK1.1 in the study by Zhang et al. is not clear because downstream targets between SGK1 and SGK1.1 are distinct (Zhang et al., 2014; Artega et al., 2008). Another possibility is that SGKs expressed in non-neuronal cells play more important roles during and/or after ischemic brain injury than those of neuronal cells. In this case, assuming that SGK activity in certain non-neuronal cells impairs brain function and overwhims neuronal SGKs (including SGK1), SGK inhibitors would behave as shown in our study. In fact, although all SGK subunits are expressed in the brain (Lang et al., 2006), their detailed distribution and function have only been minimally examined. There are reports that designate the apparent existence of SGK1 in neurons, astrocytes, and oligodendrocytes (Lang et al., 2006). In contrast, Wärttges et al. (2002) showed the existence of SGK1 in a minor proportion of brain microglia. Indeed, in support of this, Zhang et al. (2015) identified a possible role of endothelial SGK1 in high salt-dependent exacerbation of brain ischemia. Thus, to obtain a comprehensive understanding of SGK operation in ischemic brain injury, certain areas still need to be elucidated. This resolution may contribute to the development of new therapeutic drugs not only for ischemic brain injury but also for other neurological disorders. Development of specific inhibitors for each SGK isoform might also help more profound explication, and these inhibitors may become greater candidates for future therapeutic strategies.

Summary: Our new findings suggest that SGK activity exacerbates ischemic brain injury, and that SGK inhibitors may be useful candidates for a stroke therapeutic strategy. Although we are not clear at this point how critical the discussed experimental disparities are, they may need to be overcome to determine the effect of SGKs on ischemic brain injury. Although SGK inhibitors are still far from clinical application because of unknown and unsolved issues, such as their ability to cross the blood-brain barrier and development of non-invasive administration, it is worth investigating the further significances of these targets for future application.

Figure 1

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