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COMMENTARY

Flavonoids: some of the wisdom of sage?

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Abbreviations: $GABA_A$ receptor, γ-aminobutyric acid A receptor

Extracts from plants are used in herbal medicine as sedatives and tranquilizers. It is very likely that the active ingredients in some of these extracts are flavonoids possessing remarkable activity for γ-aminobutyric acid A ($GABA_A$) receptors. Marder, Medina, Paladini and their co-workers in Argentina played a major role in drawing attention to the central actions and therapeutic potential of flavonoids (Medina *et al*., 1997). This team of pharmacologists and medicinal chemists synthesised numerous molecules of the flavonoid type and demonstrated their structure–activity, and differing potencies at GABA-related benzodiazepine sites (Marder & Paladini, 2002).

In this issue of *BJP*, Kavvadias *et al*. (2004) describe the positive allosteric modulation of recombinant $GABA_A$ receptors by the flavonoid hispidulin (4′,5,7-trihydroxy-6-methoxyflavone). They demonstrate that hispidulin crosses the blood–brain barrier and relate this to the anticonvulsant action of hispidulin. This flavonoid was one of five compounds (two flavonoids and three terpenoids) isolated from the herb sage, using a benzodiazepine binding assay-guided fractionation (Kavvadias *et al*., 2003). Preparations of sage have been used widely in herbal medicine to assist memory (Perry *et al*., 2000), and an extract of Spanish sage has been shown to enhance memory in healthy young volunteers (Tildesley *et al*., 2003). Sage also contains α-thujone, a known $GABA_A$ receptor antagonist and a toxic component of absinthe (Hold *et al*., 2000), which may influence the GABA-enhancing effects of hispidulin and related compounds in sage extracts. The levels of α-thujone in individual sage plants are known to vary considerably (Perry *et al*., 1999).

Kavvadias *et al*. (2004) show that hispidulin (at 50 nM or higher; maximal effect at 10 μM) acts as a positive allosteric modulator across a range of $GABA_A$ receptor subtypes, including $\alpha6\beta2\gamma2S$ subtypes that are insensitive to positive modulation by diazepam. The benzodiazepine antagonist flumazenil reduced, but did not block the action of hispidulin on any of the $GABA_A$ receptor subtypes tested – data indicating that a part of the positive modulatory action of hispidulin is mediated through flumazenil-insensitive sites on $GABA_A$ receptors. As hispidulin did not influence the action of GABA on $\alpha1\beta2$ $GABA_A$ receptors, hispidulin does not interact with low-affinity flumazenil-insensitive benzodiazepine sites (Walters *et al*., 2000). Thus, there is more to hispidulin than actions on classical benzodiazepine sites on $GABA_A$ receptors consistent with flumazenil-insensitive actions of other flavonoids, for example, amentoflavone (Hanrahan *et al*., 2003), apigenin and quercetin (Goutman *et al*., 2003).

Flavonoids, structurally related to hispidulin, have been isolated from herbal preparations. 5,7-Dihydroxy-6-methoxyflavone (i.e. hispidulin lacking the 4′-hydroxy group) inhibits flunitrazepam binding at 1 μM, and on oral administration acts as a neutralising allosteric modulator blocking the anxiolytic and myorelaxant, but not the sedative and anticonvulsant effects elicited by diazepam (Huen *et al*., 2003). It is found in *Scutellaria baicalensis,* an important herb in traditional Chinese medicine. 6-Methylapigenin (4′,5,7-trihydroxy-6-methylflavone, that is, hispidulin with a methyl group replacing the methoxy group) isolated from *Valerian*, a well-known sedative herb, inhibits benzodiazepine binding at 0.5 μM in a manner suggesting that it may be a positive modulator of $GABA_A$ receptors (Wasowski *et al*., 2002). Thus, flavones substituted in the 6-position with a methoxy or methyl substituent have interesting effects on $GABA_A$ receptor function.

Flavonoids found in fruits, vegetables and plant-derived beverages have diverse pharmacological actions in the central and peripheral nervous systems (e.g. Bastianetto *et al*., 2000; Jiang & Dusting, 2003), at least some of which appear to be related to their activities as free-radical scavengers and as antioxidants. Indeed, there has been considerable recent interest in dietary strategies to combat oxidative stress-related damage in various pathophysiological conditions (Youdim & Joseph, 2001). However, flavonoids can have further diverse actions on cellular signalling mechanisms, with, for example, the green tea polyphenol, (−)-epigallocatechin-3-gallate, having multiple effects on intracellular life/death signaling cascades (Mandel *et al*., 2003). Interestingly, Kavvadias and co-workers found that ^{14}C-hispidulin entered the brain confirming earlier evidence that the lipophilicity of flavonoids allows them to cross the blood–brain barrier (Youdim *et al*., 2003).

The recent advances in our knowledge on the neuropharmacology of flavonoids suggest that they have potential for the management of various neurological and psychiatric conditions. Thus, actions of molecules such as hispidulin might be able to target $GABA_A$ receptors for the management of anxiety and epilepsy, while other flavonoids may be useful in neurodegenerative conditions. Indeed, you are what you drink and eat – food for sagacious thought?

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