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LETTER TO THE EDITOR

Cannabinoid agonist WIN-55,212-2 partially restores neurogenesis in the aged rat brain

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A decline in neurogenesis in the hippocampus may underlie age-related memory impairment in rats and humans. We now show that WIN 55,212-2 administration for 3 weeks can partially restore neurogenesis in the hippocampus of aged rats. Cannabinoid receptor stimulation therapy may thus provide clinical benefit for humans with age-associated memory impairment.

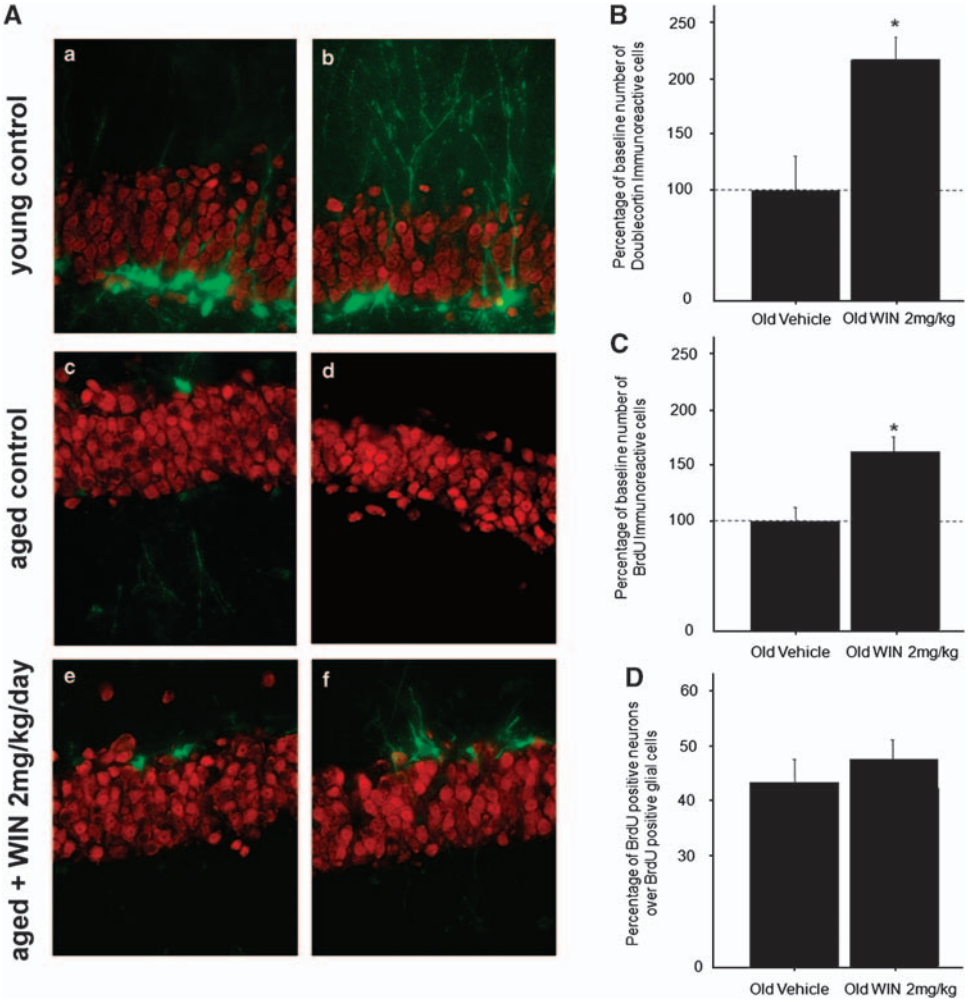

Figure 1 (**A**) Doublecortin immunoreactivity (IR) in the dentate gyrus (DG). For all pictures, Doublecortin immunoreactivity (DCX-IR) is in green and NeuN-IR is in red. (**a**, **b**) 3-month-young rats, magnification $\times 600$. (**c**, **d**) 23-month control rats, magnification $\times 600$. (**e**, **f**) 23-month-old rats treated for 3 weeks with 2 mg kg^{-1} per day of WIN-55,212-2, magnification $\times 600$. Note the significant decrease in DCX-IR between young (**a**, **b**) and aged control (**c**, **d**) rats, as well as the significant increase in DCX-IR between aged controls (**c**, **d**) and WIN-treated aged (**e**, **f**) rats. (**B**) Number of DCX-IR cells by DG: a significant increase (116%, $^*P<0.05$, Fisher's PLSD *post-hoc* test) of doublecortin immunoreactive cells was observed in the subgranular zone of the dentate gyrus of rats treated 3 weeks with 2 mg kg^{-1} per day of WIN-55,212-2. (**C**) 5-bromo-2-deoxyuridine (BrdU)-positive cells in the DG of aged animals: a significant increase (63%, $^*P<0.05$, Fisher's PLSD *post-hoc* test) of BrdU immunoreactive cells was observed in the subgranular zone of the dentate gyrus of rats treated for 3 weeks with 2 mg kg^{-1} per day of WIN-55,212-2. (**D**) Proportion of neurons/glia co-localized with BrdU cells in the DG of aged animals: no significant changes could be seen in the proportion of new neurons over new glial cells.

The endocannabinoid system regulates some aspects of the brain's inflammatory response, including the release of pro-inflammatory cytokines and modulation of microglial activation.[1–4] The endocannabinoid system is composed of two G-protein-coupled receptors designated as CB1 and CB2 expressed throughout the body and notably by neural stem cells.[5] We have previously shown that stimulation of the CB1/2 receptors using a low dose of WIN-55,212-2 significantly reversed the LPS-induced microglia activation in young rats.[2] This anti-inflammatory effect was also found in aged rats, attenuating the age-induced performance impairment observed in the water pool task.[3] As normal aging is associated with increased levels of microglial activation and a decrease in neurogenesis, both probably contributing to the hippocampus-related memory deficit, we investigated the effects of an agonist of CB1/2 receptors on neurogenesis in the brain of normal aged rats.

A total of 12 old (23-month-old) and 6 young (3-month-old) male F-344 rats were chronically infused for 28 days subcutaneously using an osmotic minipump with WIN-55,212-2 ($2\,mg\,kg^{-1}$ per day $n=6$) or the vehicle ($n=12$) into the dorsal abdominal area. Two injections of $50\,mg\,kg^{-1}$ i.p. of 5-bromo-2-deoxyuridine were made on day 1 and day 2 post surgery to track new cells' production. The rats were assigned to one of the following three groups: young-vehicle ($n=6$), old + vehicle ($n=6$) and old + WIN-55,212-2 $2\,mg\,kg^{-1}$ per day ($n=6$).

Doublecortin immunoreactivity was found only in the subgranular zone of the dentate gyrus (DG) of the hippocampus (Figure 1A). A significant difference (Figure 1Aa–d) in doublecortin immunoreactivity was found between young (3-month-old, 73.125 ± 22.8 cells per DG) and old rats (23-month-old, 3 ± 1.8 $P<0.05$). The 4 weeks of WIN 55,212-2 infusion resulted in a significant increase in doublecortin immunoreactivity cells ($+116\%$, $F_{1,30}=6.774$, $P=0.0142$, ANOVA with Fisher's PLSD *post-hoc* test) as compared with that in old vehicle-treated controls (Figure 1B).

5-bromo-2-deoxyuridine immunoreactivity was found sparsely in the cortex and hippocampus of the old vehicle-treated controls. The number of 5-bromo-2-deoxyuridine immunoreactivity cells was counted in the DG; the 4 weeks of WIN-55,212-2 infusion produced a significant increase in 5-bromo-2-deoxyuridine immunoreactivity cells ($+63\%$, $F_{1,221}=12.795$, $P=0.0004$ ANOVA with Fisher's PLSD *post-hoc* test) as compared with that in old vehicle-treated controls (Figure 1C). The proportion of newly produced neurons over glial cells was determined and showed no significant difference between control or treated aged rats (Figure 1D, $P=0.42$), confirming the increase in number of neurons engrafted in the DG after the 4-week treatment.

Our results confirm that neurogenesis is still present during normal aging in rats, although at a drastically reduced level as compared with that in young rats, for review see Verret *et al*.[6] We now report that neurogenesis in aged rats can be significantly increased by a low, continuous, non-psychoactive dose of a cannabinoid receptor agonist, WIN-55,212-2. This report shows for the first time the potential therapeutic efficacy of endocannabinoid receptor stimulation in stimulating neurogenesis from proliferation to engraftment during normal aging *in vivo*. The current results, coupled with our previous observations regarding the role of endocannabinoid receptors,[3,4] underscores the potential clinical benefits of cannabinoid pharmacotherapies during normal and pathological brain aging.

Conflict of interest

The authors declare no conflict of interest.

Author's contributions

YM and GLW conceived and designed the study. YM and HMB performed the experiments. YM, HMB and GLW wrote the paper. All authors have read and approved the final paper.

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Activation of brain interleukin-1β in schizophrenia

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The underlying pathophysiological cause of schizophrenia is essentially unknown. Increasing evidence suggests that immunological processes may contribute to the etiology of the disease. Owing to the lack of direct evidence of an infectious cause of schizophrenia much attention has been directed towards cytokines; molecules that initiate immunological