

—Review—

Characterization of Senescence-Accelerated Mouse Prone 6 (SAMP6) as an Animal Model for Brain Research

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Abstract: The senescence-accelerated mouse (SAM) was developed by selective breeding of the AKR/J strain, based on a graded score for senescence, which led to the development of both senescence-accelerated prone (SAMP), and senescence-accelerated resistant (SAMR) strains. Among the SAMP strains, SAMP6 is well characterized as a model of senile osteoporosis, but its brain and neuronal functions have not been well studied. We therefore decided to characterize the central nervous system of SAMP6, in combination with different behavioral tests and analysis of its biochemical and pharmacological properties. Multiple behavioral tests revealed higher motor activity, reduced anxiety, anti-depressant activity, motor coordination deficits, and enhanced learning and memory in SAMP6 compared with SAMR1. Biochemical and pharmacological analyses revealed several alterations in the dopamine and serotonin systems, and in long-term potentiation (LTP)-related molecules. In this review, we discuss the possibility of using SAMP6 as a model of brain function.

Key words: behavioral analysis, dopamine, NMDA receptor, SAMP6, serotonin

Introduction

The senescence-accelerated mouse (SAM) is a group of inbred mouse strains that are used as animal models of senescence acceleration and age-associated disorders. During sister-brother mating of AKR/J mice obtained from Jackson Laboratories (ME, USA) by the Department of Pathology, Chest Disease Research Institute (now the Institute for Frontier Medical Sciences), Kyoto University (Kyoto, Japan), Dr. Takeda and his colleagues became aware that most of the mice in certain litters demonstrated senescent phenotypes, presenting as a lack of activity, hair loss and lack of sheen, skin lesions, increased lordokyphosis, and premature death. Selective breeding, based on senescence scores, life span, and pathobiological phenotypes, was then carried out [66],

leading to the development of nine senescence-accelerated-prone (SAMP) strains, and three senescence-accelerated-resistant (SAMR) strains. Each SAMP strain exhibits accelerated senescence characteristics. Among these strains, SAMP8 and SAMP10 have age-related deficits in learning and memory [36, 45, 55, 56, 65, 70], emotional disorders [35, 65], and altered circadian rhythm [65]. Since these phenotypes are accelerated with aging, SAMP8 and SAMP10 are frequently used as models for studying age-related changes in higher brain function. In contrast, SAMP6 is predominantly used as a model of senile osteoporosis, since mice exhibit low bone mass, and slow bone loss [34]. After 4 months of age, SAMP6 has global low bone density [27], marrow osteogenic defects, and deficits in endocortical mineralizing surface [60], as well as reduced femoral weight,

(Received 1 August 2013 / Accepted 9 September 2013)

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Table 1. Summary of behavioral characteristics of SAMP6 compared with age-matched SAMR1.

Behavioral characteristics	Behavioral tests	Juvenile	Adult		Old	
		1 MO ^{a)}	4 MO	6 MO	8 MO	12 MO
Activity	Open field test	High *	High **		High **	
	Home cage activity test			High *		Low ^{NS}
	Y-maze test	High ^{NS b)}	High *		High **	
	Elevated plus maze test	High **	High **		High *	
	Light-dark exploration test	High **	High **		High *	
Motor coordination	Wire-hanging test (score)	Low *	Low ^{NS}		Low **	
	Wire-hanging test (time)	Low **	Low ^{NS}		Low **	
	Rotating rod test (static version)	Low **	Low ^{NS}		Low ^{NS}	
	Rotating rod test (accelerating version)	Low **	Low **		Low **	
Anxiety	Elevated plus maze test (open arm entry)	Low **	Low *		Low *	
	Elevated plus maze test (time)	Low **	Low *		Low **	
	Light-dark exploration test	Low **	Low **		Low **	
	Marble-burying test	Low *	Low **		Low **	
Depression	Tail suspension test	Low **	Low *		Low *	
Learning and Memory	Y-maze test	High ^{NS}	High *		High *	
	Novel object recognition test		High *			
	Novel object location test		High **			
	Win-shift eight-arm radial maze test		High *			
	Morris water maze (reference memory)		Similar ^{c)}		Similar	
	Morris water maze (working memory)		Low **		Low **	

*: $P < 0.05$ compared with age-matched SAMR1. **: $P < 0.01$ compared with age-matched SAMR1. a) month (s) old. b) NS: there is a tendency but no significance. c) Similar: the performance of SAMP6 is similar to that of SAMR1.

and calcium and phosphorus levels [9]. However, an aging-related increased expression of S100 β , a factor underlying the increased risk of Alzheimer's disease, in the brain of SAMP6 was reported, compared with SAMR1, suggesting possible central nervous system alterations in SAMP6 [21]. We therefore decided to study whether SAMP6 was also a model of senescence-related brain alterations and diseases.

Behavioral Characteristics

Since the bone mineral density of SAMP6 is highest at 4 months of age [27], this is thought to be the age at which these mice have their optimal body function, while the median survival time of SAMP strains is 9.7 months [66]. We therefore performed a battery of behavioral analyses using 1- (juvenile), 4–6- (adult), and 8–12-month-old (old) SAMP6 and age-matched SAMR1 to study age-related changes in behavioral characteristics (Table 1).

Open field, home cage activity, Y-maze, elevated plus maze, and light-dark exploration tests all revealed that SAMP6 exhibits higher motor activity compared with SAMR1 [40–42]. In the open field test, the distance travelled by SAMP6 in 25 min was greater than that travelled

by age-matched SAMR1 [40]. In the Y-maze test, the total number of arm entries of SAMP6 was significantly higher than age-matched SAMR1 at 4 and 8 months, while a similar trend was observed when mice were 1 month of age [41]. Similarly in the elevated plus maze test, the total number of arm entries of SAMP6 was significantly higher than age-matched SAMR1 [40]. In the light-dark exploration test, SAMP6 exhibited a significantly increased total number of transitions compared with age-matched SAMR1 [40]. Since behavioral changes are already apparent at 1 month of age, it is likely that this is an innate behavioral characteristic of SAMP6. In the home cage activity test, the total activity of 6-month-old SAMP6 during a 24-h period was significantly higher than SAMR1 [42]. In contrast, the total activity of 12-month-old SAMP6 tended to be lower than age-matched SAMR1, and was significantly lower than 6-month-old SAMP6 [42]. The higher motor activity of SAMP6 is observed until 8 months of age, after which motor activity begins to decline, and is detectably lower at 12 months of age [42].

Results of the wire hanging and rotating rod tests revealed that SAMP6 had an innate motor coordination deficit. In the wire-hanging test, the mean score and latency to fall of 1- and 8-month-old SAMP6 were sig-

nificantly lower than age-matched SAMR1 (unpublished data). In contrast, no significant difference either in the score or latency to fall off was detected between SAMP6 and SAMR1 at 4 months of age [43]. In the rotating rod test, the latency of SAMP6 to fall off an accelerating rod was significantly shorter than SAMR1 at 1–8 months of age [43 and unpublished data]. However, in a 3-rpm constant speed, 1- and 8-month-old SAMP6 tended to fall off faster than age-matched SAMR1 (unpublished data), while 4-month-old SAMP6 had improved latency [43]. Since there was no difference between the grip strength of SAMP6 and SAMR1 at 1–8 months of age [43 and unpublished data], the motor coordination deficit observed in SAMP6 is unlikely to be caused by reduced grip strength.

Reduced anxiety of SAMP6, compared with SAMR1, was revealed by results of the elevated plus maze, light-dark exploration, and marble-burying tests. In the elevated plus maze test, SAMP6 spent significantly greater periods of time on, and more frequently entered, the open arms compared with age-matched SAMR1 at 1–8 months of age [40]. In the light-dark exploration test, SAMP6 spent significantly longer in the light box than age-matched SAMR1 [40]. Finally in the marble-burying test, the number of marbles buried by SAMP6, and the length of time they spent marble-burying, were significantly higher than age-matched SAMR1 [40]. In SAMP6, the time spent on the open arms and the number of open arm entries in the elevated plus maze test were significantly decreased with aging. This suggests that there is an age-associated decrease in the difference between the anxiety levels of SAMP6 and SAMR1. In contrast, there was no age-dependent change in the time spent in the light box in the light-dark exploration test, the number of marbles buried or the time of marble-burying behavior in the marble-burying test from 1 to 8 months of age in SAMP6. The reason why SAMP6 exhibited age-associated decrease in anti-anxiety behavior in elevated plus maze test, but not in light-dark exploration or marble-burying tests, might be that elevated plus maze test gives animals stronger load compared with the other two behavioral tests and SAMP6 has an age-dependent anxiety specifically related to elevation.

The tail suspension test revealed that SAMP6 has innate anti-depressant activities compared with SAMR1. Specifically, the immobility time of SAMP6 was significantly shorter than age-matched SAMR1 at 1–8 months of age, but the difference in anti-depressant

activities gradually decreased as the mice aged [40]. However, since SAMP6 are hyperactive, it is unclear whether their shortened immobility time in the tail suspension test is specifically due to depression-related mechanisms.

The Y-maze, novel object recognition, object location, and delayed spatial win-shift eight-arm radial maze tests all revealed that SAMP6 has enhanced spatial learning and memory compared with SAMR1. In the Y-maze test, the spontaneous alteration behaviors of 4- and 8-month old SAMP6 were significantly higher, while the behavior of 1-month-old SAMP6 tended to be increased, compared with age-matched SAMR1 [41]. In the novel object recognition test, 4-month-old SAMP6 showed a significantly higher exploratory preference for the novel, rather than old, object compared with SAMR1 [41]. In the object location test, 4-month-old SAMP6 showed a significantly increased exploratory preference for the displaced object compared with age-matched SAMR1 [64]. In the delayed spatial win-shift eight-arm radial maze test, 4-month-old SAMP6 had a greater improvement in the percentage of correct choices during days 2–6 of nine consecutive days, compared with SAMR1 [64]. Overall, SAMP6 mice exhibited enhanced spatial learning and memory, and this behavioral characteristic was not affected by aging. In contrast, Liu *et al.* previously reported a working memory deficit of 4- and 8-month-old SAMP6 in the Morris water maze test compared with age-matched SAMR1 [31]. However, since the water maze and Y-maze tests measure different behavioral paradigms, these results cannot be compared directly. The Y-maze test is based on the natural tendency of mice to alternate their choice of arms, whereas the water maze test is a stress paradigm based on aversive motivation [11, 14]. It is possible that the reduced anxiety of SAMP6 [40] affects their performance in each test in a different way. In the Y-maze test, it could positively influence performance by increasing the motivation to explore, whereas in the Morris water maze test, it may negatively influence working memory, since this test uses an aversive stimulation as the reinforcer for memory.

Potential Mechanisms of Action

The neurotransmitters dopamine and serotonin control motor activity, emotional behavior, and the process of working memory [6, 10, 18, 26, 32, 52, 53, 72, 73]. In

Table 2. Concentrations of dopamine, serotonin, and their metabolites

Region	dopamine (ng/g tissue)		DOPAC (ng/g tissue)		HVA (ng/g tissue)	
	SAMR1	SAMP6	SAMR1	SAMP6	SAMR1	SAMP6
cortex	78.94 ± 13.04	189.70 ± 38.22*	34.51 ± 2.97	36.16 ± 7.40	49.03 ± 3.49	78.16 ± 10.77*
hippocampus	9.71 ± 3.05	8.99 ± 1.19	9.78 ± 2.32	11.02 ± 0.68	9.74 ± 2.16	10.81 ± 1.30
striatum	2,970.74 ± 206.82	2,672.13 ± 264.84	677.58 ± 54.96	551.19 ± 38.93	252.55 ± 10.90	353.50 ± 26.24**
Nucleus Accumbens	339.23 ± 90.00	772.49 ± 58.90**	3.69 ± 1.57	4.06 ± 0.99	58.31 ± 9.42	136.9 ± 2.35**
brain stem	54.75 ± 5.00	62.02 ± 10.37	27.86 ± 2.71	29.39 ± 3.17	52.09 ± 3.77	33.53 ± 2.14**
cerebellum	1.38 ± 0.12	2.64 ± 0.20**	0.74 ± 0.09	0.91 ± 0.18	3.28 ± 0.35	8.12 ± 0.89**

Region	3-MT (ng/g tissue)		5-HT (ng/g tissue)		5-HIAA (ng/g tissue)	
	SAMR1	SAMP6	SAMR1	SAMP6	SAMR1	SAMP6
cortex	77.39 ± 11.57	68.69 ± 14.78	249.11 ± 17.64	337.98 ± 23.00*	428.121 ± 32.016	634.85 ± 42.97**
hippocampus	4.43 ± 1.18	3.26 ± 0.70	193.30 ± 18.85	220.03 ± 18.68	777.90 ± 46.55	1,090.00 ± 64.74**
striatum	507.46 ± 42.51	582.66 ± 77.35	325.12 ± 19.14	329.93 ± 38.28	738.92 ± 55.83	1,099.21 ± 100.69*
Nucleus Accumbens	47.33 ± 17.77	167.14 ± 33.19*	285.94 ± 35.44	440.91 ± 32.19*	1,194.36 ± 68.35	1,284.98 ± 161.26
brain stem	27.90 ± 2.64	33.98 ± 3.59	481.84 ± 40.00	451.00 ± 16.12	1,423.29 ± 95.18	922.33 ± 39.30**
cerebellum	1.22 ± 0.19	1.35 ± 0.31	33.11 ± 1.03	46.39 ± 3.04**	83.23 ± 5.66	196.83 ± 12.27**

Data are expressed as mean ± SEM. * $P < 0.05$; ** $P < 0.01$.

addition, glutamate N-methyl-D-aspartate (NMDA) receptors are well known to play a role in many forms of learning and memory [7, 30, 39, 48, 51]. Among the NMDA receptor (NR) family, the NR2B subunit is crucial for long-term potentiation (LTP) [4, 17, 67, 69], while the alpha calcium/calmodulin dependent protein kinase II (CaMKII)/ NR2B-containing NMDA receptor signaling pathway is important in maintaining synaptic plasticity and spatial cognition [20, 24, 25, 59]. We therefore studied these LTP-related molecules, as well as dopamine and serotonin, in SAMP6.

Dopamine

Western blotting revealed increased expression of the dopamine-biosynthesizing enzyme tyrosine hydroxylase (TH), as well as serine-40-phosphorylated TH, in the striatum and nucleus accumbens (NAc) of 1-month-old SAMP6 compared with age-matched SAMR1 [40].

Measurement of dopamine and its metabolites using high performance liquid chromatography (HPLC) revealed that the concentrations of dopamine and homovanilic acid (HVA) in the cortex, HVA in the striatum, dopamine and HVA in the cerebellum, and dopamine, 3-methoxytyramine (3-MT), and HVA in the NAc were all significantly higher in 6-month-old SAMP6 than in SAMR1 [43 and unpublished data] (Table 2). In contrast, the concentration of HVA in the SAMP6 brainstem was significantly lower than age-matched SAMR1 [43]. Finally, increased expression of the dopamine receptor 1 (D1) and dopamine transporter (DAT) in the striatum,

dopamine receptor 3 (D3) in the NAc, and D1 and D3 in the cerebellum were seen in SAMP6 mice, as assessed by western blotting [43].

A D1 agonist, SKF82958 (6-chloro-7, 8-dihydroxy-3-allyl-1-phenyl-2, 3, 4, 5-tetrahydro-1-phenyl-1H-3-benzazepine hydrobromide), was administered to 6- and 12-month-old SAMP6, SAMR1, and AKR/J (the original strain of SAM), to compare the sensitivity of this receptor among these strains. Treatment with SKF82958 significantly increased the motor activity of 6-month-old SAMP6 compared with age-matched AKR/J and SAMR1 [42]. Moreover, the D1 sensitivity of 12-month-old AKR/J and SAMR1 was similar to their corresponding 6-month-old mice, whereas the D1 sensitivity of 12-month-old SAMP6 was significantly lower than at 6 months of age [42]. These results revealed that SAMP6 has a higher D1 sensitivity as adult, but then undergo an age-related decline.

Serotonin

Western blotting revealed elevated expression levels of the serotonin-biosynthesizing enzyme tryptophan hydroxylase (TPH), as well as serine-58-phosphorylated TPH, in the brain stem of 1-month-old SAMP6 compared with age-matched SAMR1 [40].

The measurement of serotonin and its metabolite using HPLC revealed that the concentration of serotonin in cortex, NAc, and cerebellum, and the concentration of 5-hydroxyindole acetic acid (5-HIAA) in cortex, hippocampus, striatum, and cerebellum, were all signifi-

cantly higher in 6-month-old SAMP6 compared with age-matched SAMR1 (Table 2). In contrast, the concentration of 5-HIAA in the brain stem of SAMP6 was significantly lower than SAMR1 (table 2).

The hallucinogenic chemical 1-[2, 5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI), a serotonin receptor 2A (5-HT_{2A}R) agonist, activates extracellular signal-regulated kinase 1/2 (ERK1/2) signaling accompanied by head-twitching behavior. Although DOI increased the head-twitch response in a dose-dependent manner in both 8-week-old SAMP6 and age-matched SAMR1, the responses of SAMP6 treated with 0.3 and 1.0 mg/kg DOI were significantly greater than the responses of SAMR1 administered identical doses [44]. In addition, the phospho-ERK1/2 and phospho-cAMP-responsive element-binding protein (CREB) levels in SAMP6 treated with 0.3 and 1.0 mg/kg DOI were significantly higher than SAMR1 given identical doses of DOI [44]. These results suggest that the 5-HT_{2A}-ERK1/2-CREB signaling pathway is enhanced in SAMP6.

LTP-related molecules

Four-month-old SAMP6 has increased expression of the NR2B subunit in the forebrain, and CaMKII in the hippocampus compared with age-matched SAMR1. On the other hand, there was no difference in NR1 and NR2A subunits, or the GluR1 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) [41, 64], as revealed by western blotting. In addition, increased phosphorylation of CaMKII and GluR1 was observed [64]. These results suggest that the NR2B-containing NMDA receptor and CaMKII signaling pathways are enhanced in SAMP6.

Animals treated with (\pm)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), an NMDA receptor antagonist, were subjected to the Y-maze and novel object recognition tests to determine whether NMDA receptors are associated with the enhanced short-term memory of SAMP6 [41]. In the Y-maze test, the spontaneous alternation behavior of 4-month-old SAMP6 was significantly higher than that of age-matched SAMR1 at each dose tested (0, 5, and 10 mg/kg), and was similar to the results of the Y-maze test in untreated mice. In SAMR1, treatment with 10 mg/kg CPP significantly impaired the alternation performance compared with untreated mice, while the spontaneous alternation behavior of SAMP6 was reduced only slightly after treatment with 10 mg/kg CPP. In the retention phase of the

novel object recognition test, SAMR1 injected with 10 mg/kg CPP exhibited a significantly reduced exploratory preference compared with untreated mice. While the exploratory performance of SAMP6 treated with 10 mg/kg CPP showed a tendency to be reduced, their performance was still greater than SAMR1. These results suggest that SAMP6 exhibits enhanced NMDA receptor function.

Conclusion and Perspectives

Results of the behavioral tests revealed that SAMP6 exhibits innate behavioral alterations; specifically higher motor activity, motor coordination deficit, lower anxiety, anti-depressant activity, and enhanced learning and memory. The higher motor activity of SAMP6 was observed until the adult stage, at which point motor activity began to decline. By later old ages, mice had lower motor activity, suggesting that this characteristic of SAMP6 undergoes an accelerated senescence-like pattern. The marked motor coordination deficit of SAMP6 was observed at juvenile and old ages, while a slight amelioration in the motor coordination deficit was seen in adult mice, suggesting that the motor coordination of SAMP6 also exhibits an accelerated senescence-like pattern. In contrast, the differences in anxiety and anti-depressant activity between SAMP6 and SAMR1 decreased gradually with age, suggesting that these actions of SAMP6 are a result of an alternative pattern of age-related change. No apparent age-related changes were observed in the enhanced memory of SAMP6.

The expression of TH and phosphorylated TH were increased in the striatum and NAc of juvenile SAMP6, suggesting these regions had an increase in the concentration of dopamine. In addition, the concentration of dopamine in the NAc of adult SAMP6 was significantly higher than in SAMR1. It was reported previously that increased dopamine release in the NAc is related to hyperactivity [13, 74], and this is thought to be an underlying mechanism causing the higher motor activity in SAMP6. Since D1 is known to modulate motor activity [15, 37, 50, 63, 68] and striatal D1 plays a role in locomotor activity [54], the increased expression of D1 in the striatum, coupled with an over-active D1 signaling cascade, in adult SAMP6 may also explain the higher activity of this strain. In addition, the accelerated senescence-like decrease in motor activity of old SAMP6 may be explained by the apparent decrease in the sensitivity

of D1 that was observed in aged, compared with adult, SAMP6.

Since it was reported that the injection of a D2/D3 agonist into lobules 9 and 10 of the cerebellar cortex, where D2 is not expressed [2], induced balance and motor coordination disturbance in the rotarod test [29], increased D3 expression in the cerebellum of adult SAMP6 was thought to be one of the mechanisms that contributed to the deficit in motor coordination. However, further examination of D3 expression in the cerebellum of juvenile and old SAMP6 is needed to evaluate whether altered D3 expression is involved in the accelerated senescence-like alteration of this behavior.

The expression of TPH and phosphorylated TPH were increased in the brainstem of juvenile SAMP6, suggesting elevated serotonin concentrations in the juvenile SAMP6 brain. In addition, serotonin concentrations were increased in the cortex and NAc of adult SAMP6. Since serotonin levels in the cortex and NAc are related to low anxiety and anti-depressant activity [8, 22, 23, 71], this may be a mechanism by which SAMP6 mice exhibit these behavioral changes. In addition, increased expression of D3 in the NAc may be involved in the anti-depressant activity of adult SAMP6, since the D3 receptor in NAc was reported to play a role in anti-depressant activity [12]. However, measuring the serotonin concentration and D3 expression in juvenile and old SAMP6 brains is necessary to determine whether the altered levels of serotonin and D3 are involved in the age-related changes of anxiety and anti-depressant activity in SAMP6.

The increased dopamine and serotonin concentrations in the cortex of adult SAMP6 were also thought to contribute to the enhanced memory of SAMP6, since these monoamines are known to modulate working memory [6, 10, 32, 53]. In addition, adult SAMP6 mice demonstrated increased expression of NR2B in the forebrain, and CaMKII in the hippocampus, while elevated phosphorylation of NR1 and CaMKII was also observed. Although these results suggest that these pathways may be involved in the enhanced memory of adult SAMP6, additional studies of the mechanisms and pathways involved in this behavioral property using juvenile and old SAMP6 are needed. In contrast, elevated level of S100 β was reported to cause decreased working memory [19]. The working memory deficit of SAMP6 reported by Liu *et al.* [31] might be due to an age-related increased expression of S100 β in the brain [21].

Several quantitative trait loci (QTLs) for senile-osteoporosis-related parameters were reported in SAMP6 [3, 38, 46, 47, 49, 57, 58] suggesting that the senile osteoporosis observed in SAMP6 is caused by some genetic alterations. Spontaneous genetic alteration (s) near these QTLs might have been co-fixed in SAMP6 through selective breeding, leading to the alterations in the dopamine, serotonin, and LTP-related-molecule systems as described above. Since neurotransmission systems of dopamine, serotonin, and glutamate are known to affect one another [1, 5, 16, 28, 33, 61, 62], a genetic alteration related to these neurotransmitter pathways might trigger the multiple molecular and behavioral alterations in SAMP6. Identifying QTLs for behavioral characteristics of SAMP6 is needed to elucidate the mechanisms involved.

Acknowledgments

We are extremely grateful to Dr. Chitoshi Itakura, Director of Research Resources Center, Brain Science Institute, RIKEN for suggestions, guidance, and encouragement throughout this study. We also wish to thank Prof. Shigeo Ito (Laboratory of pharmacology), Prof. Takashi Agui (Laboratory of laboratory animal science and medicine), and Prof. Kazuhiro Kimura (Laboratory of biochemistry) of Graduate School of Veterinary Medicine, Hokkaido University for their helpful discussion.

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