worm thermotolerance, prevented glucose toxicity, delayed Alzheimer's amyloid-beta toxicity and decreased Parkinson's alpha-synuclein aggregation. Interestingly, D-beta-hydroxybutyrate did not extend life span in a genetic model of dietary restriction, indicating that it is likely functioning through a similar mechanism.

21.3.3 Trichostatin A

Trichostatin A (TSA) is another widely used HDACI that demonstrates a broad spectrum of epigenetic activities, including inhibition of the cell cycle since the beginning of the growth stage and promotion of the expression of apoptosis-associated genes. TSA is recognized as a promising anticancer drug candidate. Possible mechanisms of action of this compound are induction of terminal differentiation, cell cycle arrest and apoptosis in different cancer cell lines, and thereby inhibition of tumorigenesis.[65]

The epigenetic and phenotypic effects of TSA treatment are very similar to those shown for SB treatment (Table 21.3). In *D. melanogaster*, an increase of both mean and maximum life span was observed due to both one-off and continuous treatment with 10 mkM TSA.[51,66] TSA treatment was effective both at the larval[51] and adult[66] stages and influenced the longevity of both short- and long-lived *D. melanogaster* lines, but to different extents.[51] Life span improvement affected both males and females, and in some cases was accompanied by an increase in locomotor activity (Figure 21.2).

These life-extending effects induced by the TSA treatment were accompanied by the hyperacetylation of core histone H3 in the promoter and coding regions of some chaperone genes, such as *hsp22*, *hsp26* and *hsp70*, along with up-regulation, in most cases, of both basal and inducible expression of these genes.[51,57–60,66] Modified chromatin morphology at the locus of *hsp22* was also revealed.[66] The authors suggested that the expression of chaperones can reduce the level of accumulation of damage, stimulate the repair mechanisms, and improve the cell stress resistance to create cellular and physiological environments that are favorable for longevity.

We performed an RNA-seq analysis of transcriptomes of TSA-treated and control w^{1118} males. According to our preliminary results, the following functional gene sets were associated with the differential expression in control and TSA-treated flies: (i) DNA replication; (ii) cell fate determination, differentiation and development of various organ systems, and (iii) mitochondria function and ATP synthesis. Surprisingly, up-regulation of many genes involved in development of the nervous system, heart and cuticula was revealed in TSA treated males in association with increased life span (unpublished data).

To summarize, the effects of TSA on life span seem more consistent than the effects of SB. TSA was shown to affect life span of both short/normal- and